STIC-ILL AU 415598 Y.M 10/8

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
To: STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer. I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonhson, H, 1996, Eur J Neurosci, 8(3): 494-9
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.

Thank you.

MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

STIC-ILL 8371292 415604 11/01/8

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
To: STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer. I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonhson, H, 1996, Eur J Neurosci, 8(3): 494-9.
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.
Thank you.
MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

10391366

STIC-ILL 8371189 415603 10/10/8

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
T : STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer. I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonhson, H, 1996, Eur J Neurosci, 8(3): 494-9.
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.

Thank you.

MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

9546284

STIC-ILL 415547 NPL

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
T : STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer. I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonhson, H, 1996, Eur J Neurosci, 8(3): 494-9.
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.

Thank you.
MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

STIC-ILL

QP351 . N43
Adams

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
T : STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer. I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonhson, H, 1996, Eur J Neurosci, 8(3): 494-9.
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.

Thank you.
MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

STIC-ILL

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
T : STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer. I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonnson, H, 1996, Eur J Neurosci, 8(3): 494-9.
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.

Thank you.

MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

STIC-ILL

QP351.N432
Admn

From: Davis, Minh-Tam
Sent: Tuesday, October 08, 2002 11:05 AM
To: STIC-ILL
Subject: Reprint request for 09/724524

1) Soontornniyomkij V, 1999, Acta Neuropathologica (Germany), 98(4): 345-8.
2) Hicks, RR, 1999, J Neurotrauma (United States) 16(6): 501-10.
3) Benisty, S, 1998, Neuroscience (United states), 86(3): 813-26.
4) Ferrer, I, 1998, Brain pathology (Zurich, Switzerland), 8(2): 253-61.
5) Hock, C, 1998, Neuroscience letters, 241(2-3): 151-4.
6) Jonhson, H, 1996, Eur J Neurosci, 8(3): 494-9.
7) Fenner, BM, 2001, Soc Neurosci Abstracts, 27(2): 2113.
8) Conner, B, 1996, Molecular Brain Res, 42(1): 1-17
9) Venero, JL, 2000, Exp neurology, 161(1): 38-48.
Thank you.
MINH TAM DAVIS
ART UNIT 1642, ROOM 8A01, MB 8E12
305-2008

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? s trkB
      S1    4273  TRKB
? s antibod?
      S2 1337894  ANTIBOD?
? s s1 and s2
            4273  S1
         1337894  S2
      S3     642  S1 AND S2
? s disease??
Processing
      S4 4949165  DISEASE??
? s s3 and s4
             642  S3
         4949165  S4
      S5      57  S3 AND S4
? s s5 and py<=1994
Processing
              57  S5
        25468415  PY<=1994
      S6      15  S5 AND PY<=1994
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S7      12  RD (unique items)
? t s7/3,k,ab/1-12

 7/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08435490   95197740   PMID: 7890832
  TrkA-immunoreactive profiles in the central nervous system:
colocalization with neurons containing p75 nerve growth factor receptor,
choline acetyltransferase, and serotonin.
  Sobreviela T; Clary D O; Reichardt L F; Brandabur M M; Kordower J H;
Mufson E J
  Department of Neurological Sciences, Rush Presbyterian-St. Luke's Medical
Center, Chicago, Illinois 60612.
  Journal of comparative neurology (UNITED STATES)  Dec 22 1994,
350 (4) p587-611, ISSN 0021-9967  Journal Code: 0406041
  Contract/Grant No.: AG10161; AG; NIA; AG10668; AG; NIA; AG11482; AG; NIA
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  The present investigation used an antibody directed against the
extracellular domain of the signal transducing nerve growth factor
receptor, trkA, to reveal immunoreactive perikarya or fibers within the
olfactory bulb and tubercle, cingulate cortex, nucleus accumbens, striatum,
endopiriform nucleus, septal/diagonal band complex, nucleus basalis,
hippocampal complex, thalamic paraventricular and reuniens nuclei,
periventricular hypothalamus, interpeduncular nucleus, mesencephalic
nucleus of the fifth nerve, dorsal nucleus of the lateral lemniscus,
prepositus hypoglossal nucleus, ventral cochlear nucleus, ventral lateral
tegmentum, medial vestibular nucleus, spinal trigeminal nucleus oralis,
nucleus of the solitary tract, raphe nuclei, and spinal cord.
Colocalization experiments revealed that virtually all striatal
trkA-immunoreactive neurons (> 99%) coexpressed choline acetyltransferase
(ChAT) but not p75 nerve growth factor receptor (NGFR). Within the
septal/diagonal band complex virtually all trkA neurons (> 95%) coexpressed
both ChAT and p75 NGFR. More caudally, dual stained sections revealed
numerous trkA/ChAT (> 80%) and trkA/p75 NGFR (> 95%) immunoreactive neurons
```

within the nucleus basalis. In the brainstem, raphe serotonergic neurons (45%) coexpressed trkA. Sections stained with a pan-trk **antibody** that recognizes primarily trkA, as well as **trkB** and trkC, labeled neurons within all of these regions as well as within the hypothalamic arcuate, supramammilary, and supraoptic nuclei, hippocampus, inferior and superior colliculus, substantia nigra, ventral tegmental area of T'sai, and cerebellular Purkinje cells. Virtually all of these other regions with the exception of the cerebellum also expressed pan-trk immunoreactivity in the monkey. The widespread expression of trkA throughout the central neural axis suggests that this receptor may play a role in signal transduction mechanisms linked to NGF-related substances in cholinergic basal forebrain and noncholinergic systems. These findings suggest that pharmacological use of ligands for trkA could have beneficial effects on the multiple neuronal systems that are affected in such disorders as Alzheimer's **disease**.

Dec 22 **1994**,
The present investigation used an **antibody** directed against the extracellular domain of the signal transducing nerve growth factor receptor, trkA, to...

... In the brainstem, raphe serotonergic neurons (45%) coexpressed trkA. Sections stained with a pan-trk **antibody** that recognizes primarily trkA, as well as **trkB** and trkC, labeled neurons within all of these regions as well as within the hypothalamic...

... effects on the multiple neuronal systems that are affected in such disorders as Alzheimer's **disease**.

7/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07812846 93343923 PMID: 8343154
trk immunoreactivity at neuronal dendrite and cell body.
Okazawa H; Nishiyama K; Kamei M; Washizaki K; Murayama S; Kwak S; Kanazawa I
Department of Neurology, Faculty of Medicine, University of Tokyo, Japan.
Biochemical and biophysical research communications (UNITED STATES) Jul 30 **1993**, 194 (2) p683-90, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neurotrophins homologous to the nerve growth factor (NGF) bind the neurotrophic receptors of the trk gene family. Since the target tissues release these neurotrophic factors to the neuron, it has been believed that their trophic effects are mediated by the retrograde axonal transport. However it remains an open question whether the neurotrophins act through the autocrine or the paracrine mechanisms, since the protein-level expression of trk has not been studied so far. We have made polyclonal **antibodies** against the recombinant proteins of chicken trkC and rat **trkB**. These **antibodies** showed immunoreactivity at the dendrite and the cell body of neuron. This subcellular localization strongly suggests the autocrine or the paracrine mechanism of the neurotrophic factors. At the same time, our data provide basic knowledge to decide where to deliver these neurotrophic factors in the therapy of neurodegenerative **diseases**.

Jul 30 **1993**,
... protein-level expression of trk has not been studied so far. We have made polyclonal **antibodies** against the recombinant proteins of chicken trkC and rat **trkB**. These **antibodies** showed immunoreactivity at the dendrite and the cell body of neuron. This subcellular localization strongly...

...basic knowledge to decide where to deliver these neurotrophic factors in the therapy of neurodegenerative **diseases**.
; Amino Acid Sequence; **Antibodies**; Base Sequence; Chick Embryo; Chickens; Cloning, Molecular; Electrophoresis, Polyacrylamide Gel; Glutathione Transferase--analysis--AN; Glutathione...
Gene Symbol: trk; **trkB**; trkC
Chemical Name: **Antibodies**; Membrane Glycoproteins; Membrane Proteins; Oligodeoxyribonucleotides; Receptor, Ciliary Neurotrophic Factor; Recombinant Fusion Proteins; Glutathione Transferase; Protein...

7/3,K,AB/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03560838 Genuine Article#: PM769 Number of References: 57
Title: INTRASTRIATAL INFUSIONS OF BRAIN-DERIVED NEUROTROPHIC FACTOR - RETROGRADE TRANSPORT AND COLOCALIZATION WITH DOPAMINE-CONTAINING SUBSTANTIA-NIGRA NEURONS IN RAT (Abstract Available)
Author(s): MUFSON EJ; KROIN JS; SOBREVIELA T; BURKE MA; KORDOWER JH; PENN RD; MILLER JA
Corporate Source: RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT NEUROL SCI/CHICAGO//IL/60612; RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT NEUROSURG/CHICAGO//IL/60612; RUSH PRESBYTERIAN ST LUKES MED CTR,RUSH ALZHEIMERS DIS CTR/CHICAGO//IL/60612; UNIV ILLINOIS,DEPT ANAT & CELL BIOL/CHICAGO//IL/00000; AMGEN INC/THOUSAND OAKS//CA/91320
Journal: EXPERIMENTAL NEUROLOGY, **1994**, V129, N1 (SEP), P15-26
ISSN: 0014-4886
Language: ENGLISH Document Type: ARTICLE
Abstract: The pattern of retrogradely transported BDNF, a member of the nerve growth family of neurotrophins, following intrastriatal infusion was immunohistochemically visualized within the rodent central nervous system. Human recombinant BDNF was infused at a rate of 3 mu g/h for 7 days with an Alzet 2002 minipump prior to sacrifice. Tissue immunohistochemically processed using a turkey anti-BDNF **antibody** revealed retrogradely transported BDNF within neurons located mainly within the ipsilateral frontoparietal cortex (predominantly layer V), parafascicular and posterior thalamic nuclei, and substantia nigra, pars compacta. Sections dual immunoreacted for BDNF and tyrosine hydroxylase revealed a subpopulation of dopaminergic neurons (approximately 28%) within the pars compacta which contained retrogradely transported BDNF. Experiments in which a mixture of BDNF and the retrograde tracer fluorogold were simultaneously infused for 7 days into the striatum revealed BDNF and fluorogold single-labeled neurons as well as BDNF and fluorogold dual-labeled cells within the substantia nigra, pars compacta. These observations indicate that only a subpopulation of neurons within the substantia nigra retrogradely transport BDNF following intrastriatal infusion and thus only a subpopulation of cells may be responsive to the trophic influences of BDNF. The retrograde transport of trophins, such as BDNF, represents a unique neuroanatomical tool to selectivity map the location of specific neurotrophin-responsive systems. Unraveling the trophic anatomy of BDNF will aid in understanding its role in development, degeneration, and experimental animal models of regeneration providing essential data for its use in clinical neurodegenerative disorders including Parkinson's **disease**. (C) 1994 Academic Press, Inc.

, **1994**
...Abstract: an Alzet 2002 minipump prior to sacrifice. Tissue immunohistochemically processed using a turkey anti-BDNF **antibody** revealed retrogradely transported BDNF within neurons located mainly within the ipsilateral frontoparietal cortex (predominantly layer...

...of regeneration providing essential data for its use in clinical neurodegenerative disorders including Parkinson's **disease**. (C) 1994 Academic Press, Inc.
...Identifiers--FACTOR RECEPTOR IMMUNOREACTIVITY; MESSENGER-RNA EXPRESSION; BASAL FOREBRAIN; CHOLINERGIC NEURONS; TYROSINE KINASE; SPINAL-CORD; ALZHEIMER-**DISEASE**; CELL-DEATH; **TRKB**

7/3,K,AB/4 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02640023 Genuine Article#: LR779 Number of References: 87
Title: CULTURED HIPPOCAMPAL-NEURONS SHOW RESPONSES TO BDNF, NT-3, AND NT-4, BUT NOT NGF (Abstract Available)
Author(s): IP NY; LI YP; YANCOPOULOS GD; LINDSAY RM
Corporate Source: REGENERON PHARMACEUT INC,777 OLD SAW MILL RIVERRD/TARRYTOWN//NY/10591
Journal: JOURNAL OF NEUROSCIENCE, **1993**, V13, N8 (AUG), P3394-3405
ISSN: 0270-6474
Language: ENGLISH Document Type: ARTICLE
Abstract: To investigate the possibility of neurotrophins acting directly on hippocampal neurons, we first examined expression of the trk receptors in sections of adult rat brain and in cultures of embryonic rat hippocampus, and then investigated general and specific responses of cultured hippocampal neurons to each of the neurotrophins. In situ hybridization studies indicated high levels of expression of **trkB** and trkC but not trkA in pyramidal cells, dentate granule neurons, and scattered interneurons. Cultures of embryonic day 18 (E18) hippocampal neurons were also found by Northern analysis to express ttkB and trkC but not trkA, indicating potential responsiveness to brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and NT-4, but not NGF. Phosphorylation experiments indeed showed that BDNF, NT-3, and NT-4 produced rapid tyrosine phosphorylation of Trk proteins, as detected by immunoprecipitation using a pan-Trk-specific **antibody** , whereas NGF produced no detectable tyrosine phosphorylation in hippocampal cultures. Similarly, all of the neurotrophins, except NGF, induced expression of c-fos mRNA and c-fos protein in these cultures. c-Fos protein induction was detectable in approximately 40-50% of the cells. While we observed no major effect of any of the neurotrophins upon the survival of E18 hippocampal neurons, BDNF, NT-3, and NT-4, but not NGF, produced marked increases in the number of neurons expressing detectable levels of either calbindin or AChE. NT-3 produced the greatest increase in the number of calbindin-positive neurons, whereas BDNF and NT-4 produced the greater increase in the number of AChE-positive neurons. Our results suggest that several of the neurotrophins have important effects in the differentiation and maintenance of function of subpopulations of hippocampal neurons.

, **1993**
...Abstract: to each of the neurotrophins. In situ hybridization studies indicated high levels of expression of **trkB** and trkC but not trkA in pyramidal cells, dentate granule neurons, and scattered interneurons. Cultures...
...rapid tyrosine phosphorylation of Trk proteins, as detected by immunoprecipitation using a pan-Trk-specific **antibody**, whereas NGF produced no detectable tyrosine phosphorylation in hippocampal cultures. Similarly, all of the neurotrophins...
...Identifiers--NEUROTROPHIC FACTOR; TRK PROTOONCOGENE PRODUCT; MESSENGER-RNA EXPRESSION; DISPERSED CELL-CULTURE; IMMEDIATE-EARLY GENES; ALZHEIMERS-**DISEASE**; MOLECULAR-CLONING
...Research Fronts: SPINAL-CORD NEURONS; RAT HIPPOCAMPUS)
91-0101 001 (AMYLOID PRECURSOR PROTEIN; EARLY ONSET FAMILIAL ALZHEIMERS-**DISEASE**; HUMAN BRAIN)

91-7695 001 (BASIC FIBROBLAST GROWTH-FACTOR; RECEPTOR-MEDIATED RETROGRADE TRANSPORT IN CNS...

7/3,K,AB/5 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02111085 Genuine Article#: KB684 Number of References: 35
Title: EFFECT OF CIGARETTE-SMOKING ON SALIVARY EPIDERMAL GROWTH-FACTOR (EGF) AND EGF RECEPTOR IN HUMAN BUCCAL MUCOSA (Abstract Available)
Author(s): WANG SL; MILLES M; WUWANG CY; MARDIROSSIAN G; LEUNG C; SLOMIANY A; SLOMIANY BL
Corporate Source: UNIV MED & DENT NEW JERSEY,NEW JERSEY DENT SCH,RES CTR,UNIV HEIGHTS,110 BERGEN ST/NEWARK//NJ/07103; UNIV MED & DENT NEW JERSEY,NEW JERSEY DENT SCH,DEPT ORAL & MAXILLOFACIAL SURG/NEWARK//NJ/07103; UNIV MED & DENT NEW JERSEY,NEW JERSEY MED SCH,DEPT ANAT/NEWARK//NJ/07103
Journal: TOXICOLOGY, **1992**, V75, N2 (NOV 1), P145-157
ISSN: 0300-483X
Language: ENGLISH Document Type: ARTICLE
Abstract: The mouth acts as a primary target for cigarette smoke which is associated with several oral **diseases** and cancer. The present study investigated the effect of cigarette smoking on salivary EGF and the buccal EGF receptor. Samples of whole saliva and buccal biopsy were obtained from 15 healthy volunteers (10 smokers and 5 non-smokers). The smokers smoked 20 or more cigarettes/day for more than 5 years. Salivary cotinine (a major metabolite of nicotine) was determined by radioimmunoassay (RIA). The salivary cotinine level was consistent with the self-reported smoking status (smokers, 106-530 ng/ml saliva; non-smokers, < 2 ng/ml saliva). As compared to the non-smokers, the salivary EGF concentration (determined by RIA) was 32% lower in those smokers whose salivary cotinine level was 250 ng/ml or higher (non-smokers, 2.21 +/- 0. 16; smokers, 1.57 +/- 0.09 ng/ml saliva; mean +/- S.E.M., P < 0.01). There was no significant difference in I-125-labeled EGF binding to the buccal receptor between the two groups. However, EGF stimulated the autophosphorylation of a 170-kDa protein band in the sample of non-smokers, but not in the smokers. The immunoblot analysis using anti-EGF receptor **antibody** indicated that the smoking-related deficiency in EGF receptor autophosphorylation was due to the functional alteration of the receptor proteins. In conclusion, cigarette smoking reduces the salivary EGF level and impairs the function of buccal EGF receptor, which may be associated with the pathology of smoking-related oral **disease**.

, **1992**
...Abstract: mouth acts as a primary target for cigarette smoke which is associated with several oral **diseases** and cancer. The present study investigated the effect of cigarette smoking on salivary EGF and ...
...of non-smokers, but not in the smokers. The immunoblot analysis using anti-EGF receptor **antibody** indicated that the smoking-related deficiency in EGF receptor autophosphorylation was due to the functional...

...of buccal EGF receptor, which may be associated with the pathology of smoking-related oral **disease**.
Research Fronts: 90-3735 002 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)

7/3,K,AB/6 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02100509 Genuine Article#: KA963 Number of References: 120
Title: BIOCHEMICAL-STUDY OF CYST FLUID IN HUMAN BREAST CYSTIC-**DISEASE** - A REVIEW (Abstract Available)
Author(s): ENRIORI CL; NOVELLI JE; CREMONA MD; HIRSIG RJP; ENRIORI PJ
Corporate Source: LAB ANAL CLIN,CORDOBA 2077/RA-1120 BUENOS AIRES//ARGENTINA/; HOSP FRANCES RIOSA,SERV GINECOL & MASTOL/BUENOSAIRES//ARGENTINA/; HOSP COSME ARGERICH,SERV CIRUGIA/BUENOS AIRES//ARGENTINA/
Journal: BREAST CANCER RESEARCH AND TREATMENT, **1992**, V24, N1, P1-9
ISSN: 0167-6806
Language: ENGLISH Document Type: REVIEW
Abstract: Gross cystic **disease** of the breast may sometimes indicate an increased risk of breast cancer. Biochemical analysis of the cyst fluid could suggest which cysts are associated with breast cancer risk, as well as providing insights into the pathophysiology of this condition. The Na+/K+ ratio appears to be associated with the histological classification of the cyst. Sulfoconjugated estrogens and androgens, especially DHEA-S, are often found at high levels. A number of gross cystic **disease** fluid proteins (GCDFPs) have been described, and several polypeptide growth factors including EGF and IGF-I are frequently found. It is hoped that biochemical analysis of these components of breast cyst fluids will shed further light on the role of gross cysts in relation to breast cancer.

Title: BIOCHEMICAL-STUDY OF CYST FLUID IN HUMAN BREAST CYSTIC-**DISEASE** - A REVIEW
, **1992**
Abstract: Gross cystic **disease** of the breast may sometimes indicate an increased risk of breast cancer. Biochemical analysis of...

...androgens, especially DHEA-S, are often found at high levels. A number of gross cystic **disease** fluid proteins (GCDFPs) have been described, and several polypeptide growth factors including EGF and IGF ...
...Identifiers--EPIDERMAL-GROWTH-FACTOR; TERM TISSUE-CULTURE; FACTOR-I; HUMAN-MILK; FIBROCYSTIC **DISEASE**; FACTOR RECEPTORS; SOMATOMEDIN-C; CANCER-CELLS; HUMAN-PLASMA; DEHYDROEPIANDROSTERONE-SULFATE
...Research Fronts: PEPTIDE SECRETION)
90-3735 002 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)
90-7814 002 (EPIDERMAL GROWTH-FACTOR RECEPTOR; MONOCLONAL EGFR1 **ANTIBODY** IN PRIMARY BREAST-CANCER PATIENTS; C-ERBB2 EXPRESSION)
90-2019 001 (NODE-NEGATIVE BREAST-CANCER...

7/3,K,AB/7 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02029316 Genuine Article#: JU805 Number of References: 30
Title: FUNCTIONAL-CHANGES IN SALIVARY-GLANDS OF AUTOIMMUNE **DISEASE** -PRONE NOD MICE (Abstract Available)
Author(s): HU YF; NAKAGAWA Y; PURUSHOTHAM KR; HUMPHREYSBEHER MG
Corporate Source: UNIV FLORIDA,HLTH SCI CTR,DEPT ORAL BIOL,POB 100424/GAINESVILLE//FL/32610; UNIV FLORIDA,HLTH SCI CTR,DEPT ORAL BIOL,POB 100424/GAINESVILLE//FL/32610; UNIV FLORIDA,HLTH SCI CTR,DEPT PHARMACOL & THERAPEUT/GAINESVILLE//FL/32610
Journal: AMERICAN JOURNAL OF PHYSIOLOGY, **1992**, V263, N4 (OCT), P E607-E614
ISSN: 0002-9513
Language: ENGLISH Document Type: ARTICLE
Abstract: Lymphocytic infiltration of the salivary glands in autoimmune **diseases** results in the human condition known as xerostomia. To

date, an animal model for the autoimmune development of salivary gland dysfunction has yet to be described. With the autoimmune diabetes-prone nonobese diabetic (NOD) mouse strain, salivary flow rates and total saliva protein concentration in both male and female mice showed a progressive decline in the nondiabetic and diabetic states. Submandibular gland weight decreased from control mice with the progression to onset of diabetes in both sexes, whereas the weight of the parotid gland remained unchanged. The level of saliva amylase activity, when measured relative to unit volume, decreased in nondiabetic males but increased upon onset of diabetes to control values. When expressed relative to protein concentration in saliva, amylase activity was depressed for both sets of NOD mice but was higher upon diabetes onset than in the nondiabetic animals. In females a similar pattern was observed except that amylase activity expressed relative to unit volume was not significantly depressed in either set of NOD mice. The same observations were made for glandular amylase activity. The level of epidermal growth factor (a product of the ductal cells of the submandibular gland) was reduced over 500- and 18-fold for male and female diabetic mice, respectively. Sodium dodecyl sulfate polyacrylamide gels of total saliva showed changes in mobility as well as concentration of several proteins in the NOD mice. Histological analysis suggests that salivary gland functional changes were not due to an acute inflammatory response but more accurately reflects changes due to chronic lymphocytic infiltration and glandular disorganization as a consequence of the autoimmune response. The NOD mouse should, therefore, serve as a model for the study of autoimmune sialoadenitis with its implications on human oral health.

Title: FUNCTIONAL-CHANGES IN SALIVARY-GLANDS OF AUTOIMMUNE **DISEASE** -PRONE NOD MICE
, **1992**
Abstract: Lymphocytic infiltration of the salivary glands in autoimmune **diseases** results in the human condition known as xerostomia. To date, an animal model for the...
...Identifiers--EPIDERMAL GROWTH-FACTOR; EXPERIMENTAL AUTOALLERGIC SIALADENITIS; PAROTID-GLAND; LEW RAT; INSULIN; **ANTIBODIES**; INDUCTION; MEMBRANE; PROTEINS
...Research Fronts: HSP70 FAMILY)
90-3735 001 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)

7/3,K,AB/8 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01986396 Genuine Article#: JR828 Number of References: 23
Title: IMMUNOHISTOCHEMICAL DEMONSTRATION OF EPIDERMAL GROWTH-FACTOR RECEPTORS IN NORMAL, BENIGN AND MALIGNANT THYROID TISSUES (Abstract Available)
Author(s): MIZUKAMI Y; NONOMURA A; MICHIGISHI T; YOKOYAMA K; NOGUCHI M; HASHIMOTO T; NAKAMURA S; MATSUBARA F
Corporate Source: KANAZAWA UNIV HOSP,PATHOL SECT,13-1 TAKARA MACHI/KANAZAWA 920//JAPAN/; KANAZAWA UNIV HOSP,DEPT NUCL MED/KANAZAWA 920//JAPAN/; KANAZAWA UNIV HOSP,DEPT SURG/KANAZAWA 920//JAPAN/; KANAZAWA UNIV HOSP,DEPT INTERNAL MED/KANAZAWA 920//JAPAN/; KANAZAWA UNIV HOSP,DEPT LAB MED/KANAZAWA 920//JAPAN/
Journal: INTERNATIONAL JOURNAL OF ONCOLOGY, **1992**, V1, N3 (AUG), P 331-335
ISSN: 1019-6439
Language: ENGLISH Document Type: ARTICLE
Abstract: Human epidermal growth factor receptor (EGF-receptor) has been detected immunohistochemically in normal, benign and malignant human thyroid tissues. With a monoclonal **antibody** for EGF-receptor and

avidin-biotin-peroxidase complex (ABC), the expression of EGF-receptor was evaluated in paraffin-embedded sections. Carcinomas of the thyroid showed a moderate to intense staining for EGF-receptor in most cases. Apical cell surface and cytoplasmic staining was the most common pattern of immunoreactivity. Adenomas showed a variable positivity in the cytoplasm of th tumor cells, and their apical cell surface staining was generally negative to borderline. The follicular cells in Hashimoto's thyroiditis showed a weak to moderate cytoplasmic staining, but those in Graves' **disease** and normal thyroids showed an essentially negative cytoplasmic staining. Apical cell surface staining was essentially negative or borderline in these benign lesions. There were no significant correlations between EGF-receptor expression and tumor size, degree of invasion or cervical metastases in the thyroid carcinomas. The apical surface expression of EGF-receptor was characteristic to thyroid carcinomas and this feature may be useful in the differentiation of thyroid carcinomas from benign thyroid lesions.

, **1992**

...Abstract: has been detected immunohistochemically in normal, benign and malignant human thyroid tissues. With a monoclonal **antibody** for EGF-receptor and avidin-biotin-peroxidase complex (ABC), the expression of EGF-receptor was...

...in Hashimoto's thyroiditis showed a weak to moderate cytoplasmic staining, but those in Graves' **disease** and normal thyroids showed an essentially negative cytoplasmic staining. Apical cell surface staining was essentially...

Research Fronts: 90-3735 001 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)
90-7814 001 (EPIDERMAL GROWTH-FACTOR RECEPTOR; MONOCLONAL EGFR1 **ANTIBODY** IN PRIMARY BREAST-CANCER PATIENTS; C-ERBB2 EXPRESSION)

7/3,K,AB/9 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01889160 Genuine Article#: JJ238 Number of References: 23
Title: EXPRESSION OF EGF, TGF-ALPHA AND EGFR IN SQUAMOUS-CELL LUNG CARCINOMAS (Abstract Available)
Author(s): GORGOULIS V; ANINOS D; MIKOU P; KANAVAROS P; KARAMERIS A; JOARDANOGLOU J; RASIDAKIS A; VESLEMES M; OZANNE B; SPANDIDOS DA
Corporate Source: NATL HELLENIC RES FDN,INST BIOL RES & BIOTECHNOL,48 VAS CONSTANTINOU AVE/GR-11635 ATHENS//GREECE/; NATL HELLENIC RES FDN,INST BIOL RES & BIOTECHNOL,48 VAS CONSTANTINOU AVE/GR-11635 ATHENS//GREECE/; GEN MIL HOSP 401/ATHENS//GREECE/; EVANGELISMOS MED CTR/GR-140 ATHENS//GREECE/; UNIV CRETE,SCH MED/IRAKLION//GREECE/; RED CROSS HOSP/ATHENS//GREECE/; UNIV ATHENS,SOTIRA HOSP,SCH MED,DEPT PULM/ATHENS//GREECE/; BEATSON INST CANC RES/GLASGOW G61 1BD//SCOTLAND/
Journal: ANTICANCER RESEARCH, **1992**, V12, N4 (JUL-AUG), P1183-1188
Language: ENGLISH Document Type: ARTICLE
Abstract: Immunohistochemical study of epidermal growth factor (EGF), epidermal growth factor receptor (EGFR) and transforming growth factor-alpha (TGF-alpha) expression was performed on paraffin-embedded tissue specimens of 70 squamous cell lung carcinomas. The carcinomas were placed to one of the following eight groups, according to the results of EGF, TGF-alpha and EGFR expression: group 1: none, group 2: only EGFR, group 3: EGFR and TGF-alpha, group 4: EGFR and EGF, group 5: TGF-alpha and EGF, group 6: all three, group 7: only TGF-alpha and finally group 8: only EGF. Statistical analysis of the results revealed that the ratio of squamous cell lung carcinomas with lymph node metastasis was significantly higher in groups 4, 5 and 6 ($P<0.01$). We also examined whether EGF receptors were truncated with the use of two monoclonal **antibodies** directed against different portions of the

receptor (EGFR1 and F4). No truncated EGF receptors were detected. These results suggest that lung carcinomas expressing the molecules EGF/EGFR, TFG-alpha/EGFR or TGF/alpha/EGF/EGFR display pathologic features of more aggressive **disease**.

, **1992**
...Abstract: 01). We also examined whether EGF receptors were truncated with the use of two monoclonal **antibodies** directed against different portions of the receptor (EGFR1 and F4). No truncated EGF receptors were...

...EGFR, TFG-alpha/EGFR or TGF/alpha/EGF/EGFR display pathologic features of more aggressive **disease**.
...Research Fronts: MAMMALIAN GENE)
90-3735 001 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)

7/3,K,AB/10 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01645560 Genuine Article#: HN847 Number of References: 39
Title: IMMUNOREACTIVE EGF IN HUMAN BENIGN PROSTATIC HYPERPLASIA - RELATIONSHIPS WITH ANDROGEN AND ESTROGEN-RECEPTORS (Abstract Available)
Author(s): LUBRANO C; SCIARRA F; SPERA G; PETRANGELI E; TOSCANO V; ROMBOLA N; PALLESCHI F; PALMA E; DISILVERIO F
Corporate Source: UNIV ROME LA SAPIENZA,IST CLIN MED 5/I-00161 ROME//ITALY/ ; UNIV ROME LA SAPIENZA,CNR,IST TECNOL BIOMED/I-00161 ROME//ITALY/; UNIV ROME LA SAPIENZA,DIPARTIMENTO UROL/I-00161ROME//ITALY/
Journal: JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, **1992** , V41, N3-8 (MAR), P683-687
Language: ENGLISH Document Type: ARTICLE
Abstract: Benign prostatic hyperplasia (BPH) is a sex steroid dependent **disease**. Estrogens and androgens can modulate in different mammalian tissues epidermal growth factor (EGF) production and/or secretion. In order to clarify the relationships between estrogen and androgen receptor concentrations and those of immunoreactive EGF (irEGF), we have evaluated these parameters in 14 human BPH samples, by means of a dextran-coated charcoal method and radioimmunoassay, respectively. Cytosolic steroid receptors did not seem to correlate with irEGF. A linear significative relationship was evident between nuclear androgen receptor (ARn) levels and endogenous irEGF but not between nuclear estrogen receptors and irEGF: in ARn negative BPH samples, irEGF levels were lower than in ARn positive ones. Therefore, it is possible that androgens act at prostatic tissue level, through their own receptors, by modulating EGF production and/or secretion.

, **1992**
Abstract: Benign prostatic hyperplasia (BPH) is a sex steroid dependent **disease**. Estrogens and androgens can modulate in different mammalian tissues epidermal growth factor (EGF) production and...
...Research Fronts: HSP70 FAMILY)
90-3735 001 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)
90-5135 001 (HUMAN BENIGN PROSTATIC HYPERPLASIA; EPIDERMAL GROWTH-FACTOR; DIFFERENTIAL REGULATION)
90-7814 001 (EPIDERMAL GROWTH-FACTOR RECEPTOR; MONOCLONAL EGFR1 **ANTIBODY** IN PRIMARY BREAST-CANCER PATIENTS; C-ERBB2 EXPRESSION)

7/3,K,AB/11 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01505792 Genuine Article#: HD735 Number of References: 30
Title: ABNORMAL EXPRESSION OF EPIDERMAL GROWTH-FACTOR RECEPTOR IN CUTANEOUS EPITHELIAL TUMORS (Abstract Available)
Author(s): GROVES RW; ALLEN MH; MACDONALD DM
Corporate Source: UNITED MED & DENT SCH GUYS & ST THOMAS HOSP,GUYS HOSP,DEPT DERMATOL,APPL DERMATOPATHOL LAB/LONDON SE1 9RT//ENGLAND/; UNITED MED & DENT SCH GUYS & ST THOMAS HOSP,GUYS HOSP,DEPT DERMATOL,APPL DERMATOPATHOL LAB/LONDON SE1 9RT//ENGLAND/
Journal: JOURNAL OF CUTANEOUS PATHOLOGY, **1992**, V19, N1 (FEB), P66-72
Language: ENGLISH Document Type: ARTICLE
Abstract: Epidermal growth factor (EGF) and transforming growth factor alpha (TGF-alpha) are important keratinocyte mitogens. Their effects are mediated by a cell membrane receptor (EGFR), quantitative and qualitative abnormalities of which may be responsible for deranged keratinocyte proliferation and differentiation. We have therefore examined EGFR expression immunohistochemically in a variety of benign and malignant epithelial neoplasms using monoclonal **antibodies** to the extracellular and intracellular receptor domains. In benign tumors (virus wart, seborrhoeic keratosis, keratoacanthoma), there was an ordered pattern of EGFR expression. In malignant tumours (basal and squamous cell carcinoma), there was loss of membrane labelling and cytoplasmic accumulation of the receptor. In premalignant proliferations, there was loss of membrane receptor with either absent cytoplasmic EGFR (actinic keratosis) or cytoplasmic receptor accumulation (Bowen's **disease**). Evidence of truncated receptors was not found. We suggest that dysregulation of the EGFR may be important in the development of cutaneous epithelial malignancies but that grossly abnormal forms of the receptor do not occur.

, **1992**
...Abstract: examined EGFR expression immunohistochemically in a variety of benign and malignant epithelial neoplasms using monoclonal **antibodies** to the extracellular and intracellular receptor domains. In benign tumors (virus wart, seborrhoeic keratosis, keratoacanthoma...

...membrane receptor with either absent cytoplasmic EGFR (actinic keratosis) or cytoplasmic receptor accumulation (Bowen's **disease**). Evidence of truncated receptors was not found. We suggest that dysregulation of the EGFR may...
...Identifiers--MONOCLONAL-**ANTIBODY**; FACTOR BINDING; EGF RECEPTOR; FACTOR-ALPHA; TUMORS; KERATINOCYTES; CARCINOMAS; SKIN; DIFFERENTIATION; AMPLIFICATION
...Research Fronts: MAMMALIAN GENE)
90-3735 001 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)
90-5229 001 (EPIDERMAL GROWTH-FACTOR; EGF TGF-ALPHA RECEPTOR IN SKIN...

7/3,K,AB/12 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01397199 Genuine Article#: GW263 Number of References: 309
Title: DIAGNOSTIC UTILITY OF ONCOGENES AND THEIR PRODUCTS IN HUMAN CANCER
Author(s): MCKENZIE SJ
Corporate Source: APPL BIOTECHNOL INC,80 ROGERS ST/CAMBRIDGE//MA/02142
Journal: BIOCHIMICA ET BIOPHYSICA ACTA, **1991**, V1072, N2-3 (DEC 10), P 193-214
Language: ENGLISH Document Type: REVIEW

, **1991**

...Research Fronts: 90-1285 002 (BONE-MARROW TRANSPLANTATION; POLYMERASE CHAIN-REACTION; CHRONIC MYELOGENOUS LEUKEMIA; GRAFT-VERSUS-HOST **DISEASE**)
90-7814 002 (EPIDERMAL GROWTH-FACTOR RECEPTOR; MONOCLONAL EGFR1 **ANTIBODY** IN PRIMARY BREAST-CANCER PATIENTS; C-ERBB2 EXPRESSION)
90-8054 002 (RAS ONCOGENES; EXPRESSION OF...

...PRECISE IDENTIFICATION)
90-3735 001 (EPIDERMAL GROWTH-FACTOR; EXPRESSION OF THE TYROSINE KINASE RECEPTOR GENE **TRKB**; MURINE KIDNEY MEMBRANES)
90-3928 001 (TYROSINE PHOSPHORYLATION; T-CELL ACTIVATION; INTERLEUKIN-2 INTERLEUKIN-2...
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? ds

Set     Items   Description
S1       4273   TRKB
S2    1337894   ANTIBOD?
S3        642   S1 AND S2
S4    4949165   DISEASE??
S5         57   S3 AND S4
S6         15   S5 AND PY<=1994
S7         12   RD (unique items)
? s neurodegenerat?
      S8   38776  NEURODEGENERAT?
? s s1 and s8
            4273  S1
           38776  S8
      S9     101  S1 AND S8
? s review
     S10  640863  REVIEW
? s s9 and s10
             101  S9
          640863  S10
     S11       3  S9 AND S10
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S12       2  RD (unique items)
? t s12/3,k,ab/1-2

 12/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07735063   93261547   PMID: 8492907
  Systemic interleukin-1 beta decreases brain-derived neurotrophic factor
messenger RNA expression in the rat hippocampal formation.
  Lapchak P A; Araujo D M; Hefti F
  Division of Neurogerontology, Andrus Gerontology Center, University of
Southern California, Los Angeles 90089-0191.
  Neuroscience (ENGLAND)  Mar 1993,  53  (2)  p297-301,  ISSN 0306-4522
Journal Code: 7605074
  Contract/Grant No.: AG09793; AG; NIA; AG10480; AG; NIA; NS22933; NS;
NINDS
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Brain-derived neurotrophic factor is selectively expressed at relatively
high levels in the rat hippocampal formation (for review, see Ref.
12; see also Refs 8, 13, 19, 20, 27) where it is thought to be involved in
mechanisms of neurodegeneration and/or neural protection related to
the plasticity of hippocampal neurons. Functional responses to
brain-derived neurotrophic factor appear to be mediated by a tyrosine
receptor kinase B with the possible involvement of the p75 low-affinity
nerve growth factor receptor protein. Among the many characteristics of
Alzheimer's disease is an upregulation of immune mediators in and around
senile plaques in Alzheimer's disease. Recently, interleukin-1 has been
shown to be detrimental to the long-term survival of embryonic hippocampal
neurons in culture. Thus, if the same occurs in vivo, it is possible that
the accumulation of interleukin-1 in Alzheimer's disease hippocampus may be
responsible for altered hippocampal neuron synaptic plasticity. This may
occur either by a direct action of interleukin-1 on hippocampal neurons or
possibly indirectly by stimulating beta-amyloid production. Other indirect
mechanisms may involve growth or survival factors such as the neurotrophin
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brain-derived neurotrophic factor which is thought to play an important role in the plastic responses of hippocampal neurons. A recent study showed that brain-derived neurotrophic factor mRNA is selectively decreased in the dentate gyrus in Alzheimer's disease. The reason(s) for the decrease of brain-derived neurotrophic factor mRNA is not known, but one possibility may be associated with the enhanced expression of interleukin-1 in the hippocampus of Alzheimer's disease patients.(ABSTRACT TRUNCATED AT 250 WORDS)

...neurotrophic factor is selectively expressed at relatively high levels in the rat hippocampal formation (for **review**, see Ref. 12; see also Refs 8, 13, 19, 20, 27) where it is thought to be involved in mechanisms of **neurodegeneration** and/or neural protection related to the plasticity of hippocampal neurons. Functional responses to brain...
Gene Symbol: **trkb**

12/3,K,AB/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08361454 Genuine Article#: 276RY Number of References: 125
Title: The therapeutic potential of neurotrophins for the treatment of diabetic neuropathy (ABSTRACT AVAILABLE)
Author(s): Fernyhough P (REPRINT) ; Tomlinson DR
Corporate Source: UNIV MANCHESTER,SCH BIOL SCI, DIV NEUROSCI, 1-124 STOPFORD BLDG, OXFORD RD/MANCHESTER M13 9PT/LANCS/ENGLAND/ (REPRINT)
Journal: DIABETES REVIEWS, 1999, V7, N4, P300-311
ISSN: 1066-9442 Publication date: 19990000
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314
Language: English Document Type: REVIEW
Abstract: Sensory neuron dysfunction is a hallmark of symmetrical diabetic polyneuropathy: Taken together, the clinical and pathological features of this condition give a picture of a distal degeneration, with progressive loss of sensation from both myelinated and unmyelinated primary afferents. Direct consequences of hyperglycemia, such as protein glycation and exaggerated flux through the sorbitol pathway, form one level of possible etiological components. tit the nest level-links between disordered biochemistry and **neurodegeneration** -a promising candidate is impaired neurotrophic support from nerve growth factor (NGF), neurotrophin-3 (NT-3), and brain-derived neurotrophic factor (BDNF). Studies focused on unmyelinated sensory fiber dysfunction in streptozocin (STZ) induced diabetic rats have established a role for deficient NGF expression in target tissues of the lower limb. The NGF-dependent (trkA-expressing) C-fiber subpopulation of unmyelinated neurons show reduced retrograde axonal transport of NGF to the lumbar dorsal root ganglia (DRG) and reduced expression of the neuropeptides substance P and calcitonin gene-related peptide (CGRP), The majority of larger myelinated sensory fibers, Which appear to be particularly sensitive to diabetes-related dysfunction? are unresponsive to NGF and do not express the trkA receptor, indeed, the available evidence indicates that these fibers express **trkB** and/or trkC and that maintenance of their phenotype may depend on BDNF and/or NT-3, Recent studies show that target tissue expression of NT-3 and BDNF is altered and retrograde axonal transport within the sciatic nerve is depressed in STZ diabetic rats. This **review** will discuss the current status of NGF work, with special reference to recent clinical trials. Also, new developments in understanding the effects of loss of NT-3 and/or BDNF dependent neurotrophic support on large myelinated sensory fiber function will be presented.

...Abstract: one level of possible etiological components. tit the nest level-links between disordered biochemistry and **neurodegeneration** -a promising candidate is impaired neurotrophic support from nerve

growth factor (NGF), neurotrophin-3 (NT...

...do not express the trkA receptor, indeed, the available evidence indicates that these fibers express **trkB** and/or trkC and that maintenance of their phenotype may depend on BDNF and/or...

...and retrograde axonal transport within the sciatic nerve is depressed in STZ diabetic rats. This **review** will discuss the current status of NGF work, with special reference to recent clinical trials...

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Set	Items	Description
S1	4273	TRKB
S2	1337894	ANTIBOD?
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S4	4949165	DISEASE??
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S6	15	S5 AND PY<=1994
S7	12	RD (unique items)
S8	38776	NEURODEGENERAT?
S9	101	S1 AND S8
S10	640863	REVIEW
S11	3	S9 AND S10
S12	2	RD (unique items)

? t s9/3,k,ab/1-10

9/3,K,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12993074 21845436 PMID: 11855816

A discrete domain of the human **TrkB** receptor defines the binding sites for BDNF and NT-4.

Naylor Ruth L; Robertson Alan G S; Allen Shelley J; Sessions Richard B; Clarke Anthony R; Mason Grant G F; Burston Judy J; Tyler Sue J; Wilcock Gordon K; Dawbarn David

University Research Centre for Neuroendocrinology (Care of the Elderly), Bristol Royal Infirmary, Bristol, BS2 8HW, United Kingdom.

Biochemical and biophysical research communications (United States) Mar 1 2002, 291 (3) p501-7, ISSN 0006-291X Journal Code: 0372516

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

TrkB is a member of the Trk family of tyrosine kinase receptors. In vivo, the extracellular region of **TrkB** is known to bind, with high affinity, the neurotrophin protein brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4). We describe the expression and purification of the second Ig-like domain of human **TrkB** (TrkBIg(2)) and show, using surface plasmon resonance, that this domain is sufficient to bind BDNF and NT-4 with subnanomolar affinity. BDNF and NT-4 may have therapeutic implications for a variety of **neurodegenerative** diseases. The specificity of binding of the neurotrophins to their receptor **TrkB** is therefore of interest. We examine the specificity of TrkBIg(2) for all the neurotrophins, and use our molecular model of the BDNF-TrkBIg(2) complex to examine the residues involved in binding. It is hoped that the understanding of specific interactions will allow design of small molecule neurotrophin mimetics. 2002 Elsevier Science (USA).

A discrete domain of the human **TrkB** receptor defines the binding sites for BDNF and NT-4.

TrkB is a member of the Trk family of tyrosine kinase receptors. In vivo, the extracellular region of **TrkB** is known to bind, with high affinity, the neurotrophin protein brain-derived neurotrophic factor (BDNF ...

... 4). We describe the expression and purification of the second Ig-like domain of human **TrkB** (TrkBIg(2)) and show, using surface plasmon resonance, that this domain is sufficient to bind...

... with subnanomolar affinity. BDNF and NT-4 may have therapeutic implications for a variety of **neurodegenerative** diseases. The specificity of binding of the neurotrophins to their receptor **TrkB** is therefore of interest. We examine the specificity of TrkBIg(2) for all the

neurotrophins...
Descriptors: Brain-Derived Neurotrophic Factor--metabolism--ME; *Nerve Growth Factors--metabolism--ME; *Receptor, **trkB**--chemistry--CH; *Receptor, **trkB**--metabolism--ME...; Dichroism; Immunoglobulin Fragments--chemistry--CH; Kinetics; Models, Molecular; Molecular Sequence Data; Protein Structure, Tertiary; Receptor, **trkB**--isolation and purification--IP; Sequence Homology, Amino Acid; Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization...
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)
Chemical Name: Brain-Derived Neurotrophic Factor; Immunoglobulin Fragments; Nerve Growth Factors; neurotrophin 4; Receptor, **trkB**

9/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12503773 21145882 PMID: 11248116
Activation of Trk neurotrophin receptors in the absence of neurotrophins.
Lee F S; Chao M V
Department of Psychiatry, Weill Medical College of Cornell University Medical College, New York, NY 10021, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Mar 13 2001, 98 (6) p3555-60, ISSN 0027-8424
Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neurotrophins regulate neuronal cell survival and synaptic plasticity through activation of Trk receptor tyrosine kinases. Binding of neurotrophins to Trk receptors results in receptor autophosphorylation and downstream phosphorylation cascades. Here, we describe an approach to use small molecule agonists to transactivate Trk neurotrophin receptors. Activation of TrkA receptors in PC12 cells and **TrkB** in hippocampal neurons was observed after treatment with adenosine, a neuromodulator that acts through G protein-coupled receptors. These effects were reproduced by using the adenosine agonist CGS 21680 and were counteracted with the antagonist ZM 241385, indicating that this transactivation event by adenosine involves adenosine 2A receptors. The increase in Trk activity could be inhibited by the use of the Src family-specific inhibitor, PP1, or K252a, an inhibitor of Trk receptors. In contrast to other G protein-coupled receptor transactivation events, adenosine used Trk receptor signaling with a longer time course. Moreover, adenosine activated phosphatidylinositol 3-kinase/Akt through a Trk-dependent mechanism that resulted in increased cell survival after nerve growth factor or brain-derived neurotrophic factor withdrawal. Therefore, adenosine acting through the A(2A) receptors exerts a trophic effect through the engagement of Trk receptors. These results provide an explanation for neuroprotective actions of adenosine through a unique signaling mechanism and raise the possibility that small molecules may be used to elicit neurotrophic effects for the treatment of **neurodegenerative** diseases.

... molecule agonists to transactivate Trk neurotrophin receptors. Activation of TrkA receptors in PC12 cells and **TrkB** in hippocampal neurons was observed after treatment with adenosine, a neuromodulator that acts through G...

... possibility that small molecules may be used to elicit neurotrophic effects for the treatment of **neurodegenerative** diseases.
Descriptors: Nerve Growth Factors--metabolism--ME; *Receptor, trkA --metabolism--ME; *Receptor, **trkB**--metabolism--ME; *Receptors, Purinergic P1--metabolism--ME; *Signal Transduction
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 2.7.11.- (Receptor, trkA)

Chemical Name: Nerve Growth Factors; Receptors, Purinergic P1; adenosine A(2a) receptor; Adenosine; Receptor, **trkB**; Receptor, trkA

9/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11354819 21437801 PMID: 11553687
The non-peptidyl fungal metabolite L-783,281 activates TRK neurotrophin receptors.
Wilkie N; Wingrove P B; Bilsland J G; Young L; Harper S J; Hefti F; Ellis S; Pollack S J
Department of Molecular Biology, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, UK. neil wilkie@merck.com
Journal of neurochemistry (United States) Sep 2001, 78 (5) p1135-45, ISSN 0022-3042 Journal Code: 2985190R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neurotrophin binding to the extracellular surface of the Trk family of tyrosine kinase receptors leads to the activation of multiple signalling cascades, culminating in neuroregenerative effects, including neuronal survival and neurite outgrowth. Since neurotrophins themselves are not ideal drug candidates due to their poor pharmacokinetic behaviour and bioavailability, small molecule neurotrophin mimetics may be beneficial in treating a number of **neurodegenerative** disorders. The present study demonstrates that L-783,281, a non-peptidyl fungal metabolite, is capable of stimulating TrkA, B and C phosphorylation to various extents in CHO cells stably expressing human Trk receptors. L-783,281 also stimulated Trk phosphorylation in a number of rat and human primary neuronal cultures, whereas the highly similar compound, L-767,827, was without effect. Mechanistic studies utilizing transiently transfected PDGF/TrkA and TrkA/PDGF chimeras, demonstrated that L-783,281 is likely to interact with the intracellular domain of the TrkA receptor. Further investigations suggested that L-783,281 was nevertheless able to instigate receptor dimerization by binding in a non-covalent manner. Although the cytotoxicity of the compound was shown to preclude its effects in neuronal survival and neurite outgrowth assays, it is a prototype for a small molecule neurotrophin mimetic that activates Trk by interacting at a site different from the neurotrophin-binding site.

... behaviour and bioavailability, small molecule neurotrophin mimetics may be beneficial in treating a number of **neurodegenerative** disorders. The present study demonstrates that L-783,281, a non-peptidyl fungal metabolite, is...
...; CY; Neurons--metabolism--ME; Phosphorylation; Rats; Receptor, trkA --genetics--GE; Receptor, trkA--metabolism--ME; Receptor, **trkB** --genetics--GE; Receptor, **trkB**--metabolism--ME; Receptor, trkC --genetics--GE; Receptor, trkC--metabolism--ME; Signal Transduction--drug effects--DE...
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 2.7.11.- (Receptor, trkA); EC 2.7.11.- (Receptor, trkC)
Chemical Name: Hypoglycemic Agents; Indoles; L 783281; Receptors, Nerve Growth Factor; Receptor, **trkB**; Receptor, trkA; Receptor, trkC

9/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11242857 21281592 PMID: 11388410
Malonate-induced cortico-motoneuron death is attenuated by NT-4, but not by BDNF or NT-3.

Van Westerlaak M G; Bar P R; Cools A R; Joosten E A
Department of Experimental Neurology, RMI for Neurosciences, Utrecht, The Netherlands.
Neuroreport (England) May 25 2001, 12 (7) p1355-8, ISSN 0959-4965 Journal Code: 9100935
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Neurotrophins are promising candidates to slow the progression of amyotrophic lateral sclerosis (ALS), a **neurodegenerative** disease in which spinal and cortical motoneurons selectively degenerate. In a long-term in vitro model, malonate-induced toxicity and cell death of motoneurons have been demonstrated. Here we studied the neuroprotective effect of BDNF, NT-3, and NT-4 on the cell death of cortical motoneurons in an organotypic culture model after chronic mitochondrial inhibition with malonate. Our data show that NT-4 completely prevents malonate-induced toxicity, whereas BDNF or NT-3 had no neuroprotective effect. In clinical trials for ALS, predominantly focussed on the survival of spinal motoneurons, BDNF has already been tested with disappointing results; our results suggest that NT-4 may be a better neurotrophin to prevent motoneuron loss.

Neurotrophins are promising candidates to slow the progression of amyotrophic lateral sclerosis (ALS), a **neurodegenerative** disease in which spinal and cortical motoneurons selectively degenerate. In a long-term in vitro...

...; PD; Organ Culture; Pyramidal Cells--metabolism--ME; Pyramidal Cells --pathology--PA; Rats; Rats, Wistar; Receptor, **trkB**--metabolism--ME
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)
...Chemical Name: Neurotrophic Factor; Malonates; Nerve Growth Factors; Neurofilament Proteins; Neuroprotective Agents; Neurotrophin 3; neurotrophin 4; Receptor, **trkB**

9/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10911548 20450877 PMID: 10993689
Expression of Trk isoforms in brain regions and in the striatum of patients with Alzheimer's disease.
Dubus P; Faucheux B; Boissiere F; Groppi A; Vital C; Vital A; Agid Y; Hirsch E C; Merlio J P
Laboratoire d'Histologie-Embryologie, EA 2406 Universite de Bordeaux 2, Bordeaux Cedex, 33076, France.
Experimental neurology (UNITED STATES) Oct 2000, 165 (2) p285-94, ISSN 0014-4886 Journal Code: 0370712
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The TrkAII tyrosine kinase receptor differs from the TrkAI isoform by an insertion of six amino acids in the extracellular domain. We used RT-PCR to determine their respective distribution in rat and human brain. Only trkAII transcripts were detected in 12 rat brain regions, while both trkAI and trkAII transcripts were detected in the cerebellum and pituitary gland. In human, both trkAI and trkAII transcripts were detected in the frontal, temporal, and occipital cortex and thalamus, while only trkAI transcripts were detected in the hippocampus and cerebellum. In the caudate and putamen, trkAII transcripts were exclusively detected. Thereafter, we studied the expression of TrkA isoforms in the striatum of five patients with Alzheimer's disease (AD), four patients with non-AD dementia, seven patients with Parkinson's disease, and six paired nondemented elderly control individuals. In controls and non-AD patients, a constant expression

of trkAII transcripts was detected within all striatum parts. In AD patients, a heterogeneous decrease in trkAII expression was observed in the caudate, putamen, and ventral striatum, resulting either in a drop of trkAII transcript levels or in a weak coamplification of trkAII and trkAI transcripts. The alteration of TrkAII gene expression paralleled those of choline acetyltransferase. Together with previous data, this suggests that the alteration of trk gene expression could contribute to a decrease in NGF binding sites and its protective effects on cholinergic neurons of AD patients. Copyright 2000 Academic Press.

; Adult; Aged; Aged, 80 and over; Corpus Striatum--metabolism--ME; Middle Age; **Neurodegenerative** Diseases--metabolism--ME; Parkinson Disease --metabolism--ME; Protein Isoforms--metabolism--ME; Rats; Rats, Wistar; Receptor, **trkB**--metabolism--ME

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 2.7.11.- (Receptor, trkA)

Chemical Name: Protein Isoforms; Receptor, **trkB**; Receptor, trkA

9/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10711337 20256265 PMID: 10798407

Cortical degeneration in the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor **TrkB**.

Xu B; Zang K; Ruff N L; Zhang Y A; McConnell S K; Stryker M P; Reichardt L F

Department of Physiology, Howard Hughes Medical Institute, University of California, San Francisco 94143, USA.

Neuron (UNITED STATES) Apr 2000, 26 (1) p233-45, ISSN 0896-6273 Journal Code: 8809320

Contract/Grant No.: P01-16033; PHS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

To examine functions of **TrkB** in the adult CNS, **TrkB** has been removed from neurons expressing CaMKII, primarily pyramidal neurons, using Cre-mediated recombination. A floxed **trkB** allele was designed so that neurons lacking **TrkB** express tau-beta-galactosidase. Following **trkB** deletion in pyramidal cells, their dendritic arbors are altered, and cortical layers II/III and V are compressed, after which there is an apparent loss of mutant neurons expressing the transcription factor SCIP but not of those expressing Otx-1. Loss of neurons expressing SCIP requires deletion of **trkB** within affected neurons; reduction of neuronal ER81 expression does not, suggesting both direct and indirect effects of **TrkB** loss. Thus, **TrkB** is required for the maintenance of specific populations of cells in the adult neocortex.

... the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor **TrkB**.

To examine functions of **TrkB** in the adult CNS, **TrkB** has been removed from neurons expressing CaMKII, primarily pyramidal neurons, using Cre-mediated recombination. A floxed **trkB** allele was designed so that neurons lacking **TrkB** express tau-beta-galactosidase. Following **trkB** deletion in pyramidal cells, their dendritic arbors are altered, and cortical layers II/III and...

... but not of those expressing Otx-1. Loss of neurons expressing SCIP requires deletion of **trkB** within affected neurons; reduction of neuronal ER81 expression does not, suggesting both direct and indirect effects of **TrkB** loss. Thus, **TrkB** is required for the maintenance of specific populations of cells in the adult neocortex.

Descriptors: Neocortex--metabolism--ME; *Neurons--metabolism--ME;

*Pyramidal Cells--metabolism--ME; *Receptor, **trkB**--metabolism--ME; *beta-Galactosidase--metabolism--ME...; PA; Mice; Mice, Transgenic; Mutation--genetics--GE; Neocortex--pathology--PA; Nerve Growth Factors --metabolism--ME; **Neurodegenerative** Diseases--metabolism--ME; **Neurodegenerative** Diseases--pathology--PA; Neurons--pathology--PA; Receptor, **trkB**--genetics--GE; Transcription Factors--metabolism--ME
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 3.2.1.23 (beta-Galactosidase)
Chemical Name: DNA-Binding Proteins; ER81 protein; Nerve Growth Factors; Transcription Factors; Receptor, **trkB**; beta-Galactosidase

9/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10610139 20148565 PMID: 10683272
Upregulation of BDNF mRNA and **trkB** mRNA in the nigrostriatal system and in the lesion site following unilateral transection of the medial forebrain bundle.
Venero J L; Vizuete M L; Revuelta M; Vargas C; Cano J; Machado A
Departamento de Bioquimica, Bromatologia y Toxicologia, Seville, 41012, Spain.
Experimental neurology (UNITED STATES) Jan 2000, 161 (1) p38-48, ISSN 0014-4886 Journal Code: 0370712
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have performed unilateral transection of the medial forebrain bundle (MFB) and studied BDNF mRNA and **trkB** mRNA levels at different postlesion times in the nigrostriatal system by means of in situ hybridization. BDNF mRNA levels were transiently induced in the substantia nigra pars compacta at 1 day postaxotomy. The disposition of BDNF mRNA expressing cells at this postlesion time in substantia nigra mimicked that of the dopaminergic neurons expressing the mRNA for the dopamine transporter. **TrkB** mRNA levels remained unaltered in the ventral mesencephalon at the different postlesion times examined-1 to 14 days. In contrast, **trkB** mRNA levels were significantly induced in the striatum at the longer postlesion time examined-14 days-when all **neurodegenerative** events are completed. It is becoming apparent that nigral BDNF mRNA levels are anterogradely transported to its target tissue in striatum. However, following axotomy, the lesion site represents a second potential target for BDNF action. Consequently, we also analyzed the pattern of mRNA expression for BDNF and **trkB** at the lesion site where dopaminergic axons are disconnected. There, we found notable inductions of both BDNF mRNA and **trkB** mRNA levels at 4 days postaxotomy. BDNF mRNA expressing cells were confined at the site of axotomy, which coincided precisely to that showing induction of **trkB** mRNA. Altogether, our results anticipate promising trophic roles of BNDF in the injured nigrostriatal system. Copyright 2000 Academic Press.

Upregulation of BDNF mRNA and **trkB** mRNA in the nigrostriatal system and in the lesion site following unilateral transection of the...
... have performed unilateral transection of the medial forebrain bundle (MFB) and studied BDNF mRNA and **trkB** mRNA levels at different postlesion times in the nigrostriatal system by means of in situ...

... substantia nigra mimicked that of the dopaminergic neurons expressing the mRNA for the dopamine transporter. **TrkB** mRNA levels remained unaltered in the ventral mesencephalon at the different postlesion times examined-1 to 14 days. In contrast, **trkB** mRNA levels were significantly induced in the striatum at the longer postlesion time examined-14 days-when all **neurodegenerative** events are completed. It is becoming apparent that nigral BDNF mRNA levels are anterogradely

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... for BDNF action. Consequently, we also analyzed the pattern of mRNA expression for BDNF and **trkB** at the lesion site where dopaminergic axons are disconnected. There, we found notable inductions of both BDNF mRNA and **trkB** mRNA levels at 4 days postaxotomy. BDNF mRNA expressing cells were confined at the site of axotomy, which coincided precisely to that showing induction of **trkB** mRNA. Altogether, our results anticipate promising trophic roles of BNDF in the injured nigrostriatal system...

...Descriptors: Derived Neurotrophic Factor--genetics--GE; *Corpus Striatum--metabolism--ME; *Medial Forebrain Bundle--physiology--PH; *Receptor, **trkB**--genetics--GE; *Substantia Nigra--metabolism--ME...; Situ Hybridization; Medial Forebrain Bundle--surgery--SU; RNA, Messenger --metabolism--ME; Rats; Rats, Wistar; Receptor, **trkB**--metabolism--ME; Substantia Nigra--chemistry--CH; Up-Regulation--physiology--PH

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)

Chemical Name: Brain-Derived Neurotrophic Factor; RNA, Messenger; Dopamine; Receptor, **trkB**

9/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10517416 20051637 PMID: 10584248

[Nerve growth factor: possibilities and limitations of its clinical application]

Factor de crecimiento nervioso: posibilidades y limitaciones de su aplicacion clinica.

Castellanos-Ortega M R; Cruz-Aguado R; Martinez-Marti L

Departamento de Biologia Molecular, CIREN, La Habana, Cuba. mariar@neubas.sld.cu

Revista de neurologia (SPAIN) Sep 1-15 1999, 29 (5) p439-47, ISSN 0210-0010 Journal Code: 7706841

Document type: Journal Article; Review; Review, Tutorial ; English Abstract

Languages: SPANISH

Main Citation Owner: NLM

Record type: Completed

INTRODUCTION: The use of neurotrophic factors for the treatment of degenerative disorders of the nervous system opens up promising new perspectives. DEVELOPMENT: Nerve growth factor (NGF) represents the most known and studied trophic factor, which acts on sensory and sympathetic neurons of the peripheral nervous system, and on basal forebrain and striatal cholinergic neurons of the central nervous system. The specificity and trophic actions of NGF on these neuronal populations and its efficacy at preventing **neurodegeneration** have led to its proposal of evaluation in the treatment of neurological diseases such as: Alzheimer's disease, diabetic neuropathies and Huntington's diseases. Preclinical and clinical studies carried out in animal models and patients with diagnosis of these diseases have revealed satisfactory results. The difficulties of the NGF central chronic infusion, and the NGF detrimental effects arising from the stimulation of other sensitive neuronal population have stimulated active efforts for the development of more efficacious delivery strategies. Besides, it has also promoted further studies on the relation between the neuropathological stage, the dose and the effects of NGF administration. CONCLUSION: The NGF is a potential therapeutic agent in the treatment of **neurodegenerative** diseases.

... specificity and trophic actions of NGF on these neuronal populations and its efficacy at preventing **neurodegeneration** have led to its proposal of evaluation in the treatment of neurological diseases such as...

... of NGF administration. CONCLUSION: The NGF is a potential therapeutic

agent in the treatment of **neurodegenerative** diseases.
; Nerve Growth Factor--pharmacology--PD; Receptor, trkA--drug effects--DE ; Receptor, **trkB**--drug effects--DE
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 2.7.11.- (Receptor, trkA)
Chemical Name: Nerve Growth Factor; Receptor, **trkB**; Receptor, trkA

9/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10445523 99431463 PMID: 10502038
Absence of brain-derived neurotrophic factor and **trkB** receptor immunoreactivity in glia of Alzheimer's disease.
Soontornniyomkij V; Wang G; Pittman C A; Hamilton R L; Wiley C A; Achim C L
Department of Pathology (Neuropathology), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
Acta neuropathologica (GERMANY) Oct 1999, 98 (4) p345-8, ISSN 0001-6322 Journal Code: 0412041
Contract/Grant No.: NS35731; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Alterations in the neuronal expression of some neurotrophins have been shown in various **neurodegenerative** processes, particularly Alzheimer's disease (AD). Glia may up-regulate neurotrophins and their high-affinity tyrosine kinase (trk) receptors in response to neural injury. In human immunodeficiency virus type 1 (HIV-1) encephalitis, activated microglia were shown to express brain-derived neurotrophic factor (BDNF), while reactive astrocytes expressed **trkB** receptor. This observation has suggested the existence of local neurotrophic regulation between different glial populations. To characterize the glial cellular distribution of BDNF and **trkB** receptor proteins in AD, we studied selected regions of postmortem brains from four AD and three age-matched control patients by double-immunofluorescence confocal microscopy. In both groups, BDNF immunoreactivity was distributed in neuronal perikarya and neuritic processes in the neocortex and hippocampus. No BDNF immunoreactivity was observed in microglia or astrocytes within and between senile plaques of AD. Catalytic **trkB** receptor immunoreactivity was present in neuronal perikarya in the neocortex and hippocampus. Reactive astrocytes and microglia were not immunoreactive for catalytic **trkB**. The absence of BDNF and **trkB** proteins in glia in AD patients is in contrast to the finding in patients with HIV-1 encephalitis. This difference suggests that glial expression of BDNF and **trkB** proteins may be characteristic of particular disease processes, rather than merely representing a stereotyped response to any type of neural injury.

Absence of brain-derived neurotrophic factor and **trkB** receptor immunoreactivity in glia of Alzheimer's disease.
Alterations in the neuronal expression of some neurotrophins have been shown in various **neurodegenerative** processes, particularly Alzheimer's disease (AD). Glia may up-regulate neurotrophins and their high-affinity...

... activated microglia were shown to express brain-derived neurotrophic factor (BDNF), while reactive astrocytes expressed **trkB** receptor. This observation has suggested the existence of local neurotrophic regulation between different glial populations. To characterize the glial cellular distribution of BDNF and **trkB** receptor proteins in AD, we studied selected regions of postmortem brains from four AD and...

... immunoreactivity was observed in microglia or astrocytes within and

between senile plaques of AD. Catalytic **trkB** receptor immunoreactivity was present in neuronal perikarya in the neocortex and hippocampus. Reactive astrocytes and microglia were not immunoreactive for catalytic **trkB**. The absence of BDNF and **trkB** proteins in glia in AD patients is in contrast to the finding in patients with HIV-1 encephalitis. This difference suggests that glial expression of BDNF and **trkB** proteins may be characteristic of particular disease processes, rather than merely representing a stereotyped response...

Descriptors: Alzheimer Disease--metabolism--ME; *Brain-Derived Neurotrophic Factor--metabolism--ME; *Neuroglia--metabolism--ME; *Receptor, **trkB**--metabolism--ME

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)

Chemical Name: Brain-Derived Neurotrophic Factor; Receptor, **trkB**

9/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10351533 99332485 PMID: 10404406

Effects of aging and axotomy on the expression of neurotrophin receptors in primary sensory neurons.

Bergman E; Fundin B T; Ulfhake B

Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. esbjorn.bergman@neuro.ki.se

Journal of comparative neurology (UNITED STATES) Aug 2 1999, 410 (3) p368-86, ISSN 0021-9967 Journal Code: 0406041

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Aging is accompanied by declined sensory perception, paralleled by widespread dystrophic and degenerative changes in both central and peripheral sensory pathways. Several lines of evidence indicate that neurotrophic interactions are of importance for a maintained plasticity in the adult and aging nervous system, and that changes in the expression of neurotrophins and/or their receptors may underpin senile **neurodegeneration** . We have here examined the expression of neurotrophin receptor (p75NTR, trkA, **trkB**, and trkC) mRNA and protein in intact and axotomized primary sensory neurons of young adult (3 months) and aged (30 months) rats. To examine possible differences among primary sensory neuron populations, we have studied trigeminal ganglia (TG) as well as cervical and lumbar dorsal root ganglia (DRG). In intact aged rats, a decrease in trk (A/B/C) mRNA labeling densities and protein-like immunoreactivities was observed. The decrease was most pronounced in lumbar DRG. In contrast, a small, not statistically significant, increase of p75NTR expression was observed in aged DRG neuron profiles. After axotomy, a down-regulation of mRNA and protein levels was observed for all neurotrophin receptors (p75NTR, trkA, **trkB** and trkC) in both young adult and aged rats. Consistent with the higher expression levels of neurotrophin receptors in unlesioned young adult primary sensory neurons, the relative effect of axotomy was more pronounced in the young adult than aged rats. Although a decrease in mean cell profile cross-sectional areas was found during aging and after axotomy, the characteristic distribution of neurotrophin receptor expression in different populations of NRG neurons was conserved. The present findings suggest an attenuation of neurotrophic signaling in primary sensory neurons with advancing age and that the expression of p75NTR and trks is regulated differently during aging. A similar dissociation of p75NTR and trk regulation has previously been reported in other neuronal systems during aging, suggesting that there may be a common underlying mechanism. Decreased access to ligands, disturbed axon function and systemic changes in androgen/estrogen levels are discussed as inducing and/or contributing factors.

... and that changes in the expression of neurotrophins and/or their

receptors may underpin senile **neurodegeneration** . We have here examined the expression of neurotrophin receptor (p75NTR, trkA, **trkB**, and trkC) mRNA and protein in intact and axotomized primary sensory neurons of young adult...

... down-regulation of mRNA and protein levels was observed for all neurotrophin receptors (p75NTR, trkA, **trkB** and trkC) in both young adult and aged rats. Consistent with the higher expression levels...
?

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? ds

Set      Items   Description
S1        4273   TRKB
S2     1337894   ANTIBOD?
S3         642   S1 AND S2
S4     4949165   DISEASE??
S5          57   S3 AND S4
S6          15   S5 AND PY<=1994
S7          12   RD (unique items)
S8       38776   NEURODEGENERAT?
S9         101   S1 AND S8
S10     640863   REVIEW
S11          3   S9 AND S10
S12          2   RD (unique items)
? s9 and s4
Processing
          3535672  9
          4949165  S4
     S13  412349  9 AND S4
? s differential or overexpress? or underexpress?
           837588  DIFFERENTIAL
           133716  OVEREXPRESS?
             1221  UNDEREXPRESS?
     S14  966240  DIFFERENTIAL OR OVEREXPRESS? OR UNDEREXPRESS?
? s s9 amd s14
>>>Term "AMD" in invalid position
? s s9 and s14
              101  S9
           966240  S14
     S15        5  S9 AND S14
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
     S16        5  RD (unique items)
? t s16/3,k,ab/1-5

 16/3,K,AB/1     (Item 1 from file: 55)
DIALOG(R)File  55:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13373793   BIOSIS NO.: 200200002614
Distribution of trkB.tc and trkB.fl in PD and DLBD.
AUTHOR: Fenner B M(a); Hammond R R; Achim C L(a)
AUTHOR ADDRESS: (a)Pathology, Univ of Pittsburgh, Pittsburgh, PA**USA
JOURNAL: Society for Neuroscience Abstracts  27 (2):p2113 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience
San Diego, California, USA  November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Brain derived neurotrophic factor(BDNF) is abundantly expressed
  in the CNS and is considered to have the potential to be both a
  therapeutic agent and be also implicated in the progress of chronic brain
  degeneration (e.g. Parkinson's disease (PD) and dementia with lewy body
  disease(DLBD)). The effects of BNDF are mediated by its binding to either
  the truncated(trkB.tc) or full-length(trkB.fl) trkB
  receptor. We hypothesize that in response to neuronal degeneration, the
  upregulation of trkB receptors and the distribution pattern of
  full-length vs truncated isoforms will have unique features depending on
```

region and possibly underlying disease. Paraffin embedded sections of cortex, hippocampus, striatum, and substantia nigra tissue from PD, DLBD, and age matched control cases were analyzed by immunohistochemistry and immunofluorescent laser confocal microscopy(IFLCM). Tissue sections were single- and double-labeled with antibodies against **trkB**.tc, **trkB**.fl, HLADR, and alpha-synuclein. Current studies analyze the localization of **trkB** in relation to tyrosine hydroxylase, dopamine transporter, and dopamine receptors. Preliminary data show extensive perivascular **trkB**.fl expression localized predominantly to microglia and to a lesser extent, astrocytes. In regions of extensive **trkB**.fl labeling, sparse neuronal labeling was observed. **TrkB** .tc localization to glial cells was also perivascular, but its distribution was punctate. There was extensive punctate localization of **trkB**.tc in the degenerating neurons of the substantia nigra and striatum. The **differential** localization of **trkB**.tc from **trkB**.fl supports the hypothesis that these receptors may perform distinct functions in **neurodegeneration**.

2001

Distribution of **trkB**.tc and **trkB**.fl in PD and DLBD.
...ABSTRACT: disease(DLBD)). The effects of BNDF are mediated by its binding to either the truncated(**trkB**.tc) or full-length(**trkB** .fl) **trkB** receptor. We hypothesize that in response to neuronal degeneration, the upregulation of **trkB** receptors and the distribution pattern of full-length vs truncated isoforms will have unique features...

...immunofluorescent laser confocal microscopy(IFLCM). Tissue sections were single- and double-labeled with antibodies against **trkB**.tc, **trkB**.fl, HLADR, and alpha-synuclein. Current studies analyze the localization of **trkB** in relation to tyrosine hydroxylase, dopamine transporter, and dopamine receptors. Preliminary data show extensive perivascular **trkB**.fl expression localized predominantly to microglia and to a lesser extent, astrocytes. In regions of extensive **trkB**.fl labeling, sparse neuronal labeling was observed. **TrkB** .tc localization to glial cells was also perivascular, but its distribution was punctate. There was extensive punctate localization of **trkB**.tc in the degenerating neurons of the substantia nigra and striatum. The **differential** localization of **trkB**.tc from **trkB**.fl supports the hypothesis that these receptors may perform distinct functions in **neurodegeneration**.
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...**trkB**.fl...

...**trkB**.tc

16/3,K,AB/2 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

13355340 BIOSIS NO.: 200100562489
Achieving specificity in Trk-neurotrophin interaction: The crystal structure of **TrkB**-d5 bound to NT-4/5.
AUTHOR: Banfield M J(a); Naylor R L; Robertson A G S; Allen S J; Brady R L (a); Dawbarn D
AUTHOR ADDRESS: (a)Biochemistry, University of Bristol, Bristol**UK
JOURNAL: Society for Neuroscience Abstracts 27 (2):p1804 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract

LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Neurotrophins such as NGF, BDNF, NT-4/5 and NT-3 exert their effects by binding to the extracellular fragments of the Trk receptor family and the p75 receptor. The Trks (TrkA, B and C) have tyrosine kinase activity and show **differential** binding affinities towards the neurotrophins such that TrkA is the high affinity receptor for NGF, **TrkB** binds NT-4/5 and BDNF, and TrkC binds NT-3 (some cross-reactivity can occur). Neurotrophin binding sites have been located to the fifth extracellular domain of the Trk receptors (d5). These domains are sufficient to both bind ligands with similar affinity to the native receptor and activate the intracellular kinase in a neurotrophin-dependent manner. We have determined the crystal structure of the **TrkB**-d5:NT-4/5 complex. The complex adopts a similar overall conformation to TrkA-d5 bound to NGF. However, there are significant differences, which include a shift in the relative orientations of the Trk domains compared to the neurotrophin, and changes in the proposed 'conserved' interaction patch. There are also changes at the 'specificity' patch where very different interactions are seen in the **TrkB**:NT-4/5 complex compared to TrkA:NGF. Comparison of these complexes reveals how specificity in Trk:neurotrophin interaction is achieved, and has implications for the design of selective treatments for **neurodegenerative** diseases.

2001

Achieving specificity in Trk-neurotrophin interaction: The crystal structure of **TrkB**-d5 bound to NT-4/5.

...ABSTRACT: the p75 receptor. The Trks (TrkA, B and C) have tyrosine kinase activity and show **differential** binding affinities towards the neurotrophins such that TrkA is the high affinity receptor for NGF, **TrkB** binds NT-4/5 and BDNF, and TrkC binds NT-3 (some cross-reactivity can...

...intracellular kinase in a neurotrophin-dependent manner. We have determined the crystal structure of the **TrkB**-d5:NT-4/5 complex. The complex adopts a similar overall conformation to TrkA-d5...

...are also changes at the 'specificity' patch where very different interactions are seen in the **TrkB**:NT-4/5 complex compared to TrkA:NGF. Comparison of these complexes reveals how specificity...

...Trk:neurotrophin interaction is achieved, and has implications for the design of selective treatments for **neurodegenerative** diseases.
DESCRIPTORS:
DISEASES: **neurodegenerative** disease...
CHEMICALS & BIOCHEMICALS: ...**TrkB**--...

...**TrkB**-d5:neurotrophin-4/5 complex
ALTERNATE INDEXING: **Neurodegenerative** Diseases (MeSH)

16/3,K,AB/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10516471 Genuine Article#: 535BU Number of References: 53
Title: Failure of brain-derived neurotrophic factor-dependent neuron survival in mouse trisomy 16 (ABSTRACT AVAILABLE)
Author(s): Dorsey SG; Bambrick LL; Balice-Gordon RJ; Krueger BK (REPRINT)
Corporate Source: Univ Maryland,Sch Med, Dept Physiol,655 W Baltimore St/Baltimore//MD/21201 (REPRINT); Univ Maryland,Sch Med, Dept

Physiol,Baltimore//MD/21201; Univ Maryland,Sch Med, Dept Anesthesiol,Baltimore//MD/21201; Univ Maryland,Sch Nursing,Baltimore//MD/21201; Univ Maryland,Program Neurosci,Baltimore//MD/21201; Univ Penn,Sch Med, Dept Neurosci,Philadelphia//PA/19104
Journal: JOURNAL OF NEUROSCIENCE, 2002, V22, N7 (APR 1), P2571-2578
ISSN: 0270-6474 Publication date: 20020401
Publisher: SOC NEUROSCIENCE, 11 DUPONT CIRCLE, NW, STE 500, WASHINGTON, DC 20036 USA
Language: English Document Type: ARTICLE
Abstract: The neurotrophin, brain derived neurotrophic factor (BDNF), exerts multiple effects on the development and maintenance of the nervous system, including regulating synaptic plasticity and promoting neuron survival. Here we report the selective failure of BDNF-dependent survival in cultured hippocampal neurons from the trisomy 16 (Ts16) mouse, an animal model of Down syndrome. This failure is accompanied by **overexpression** of a truncated, kinase-deficient isoform (T1) of the BDNF receptor tyrosine receptor kinase B (**trkB**). Adenovirus-mediated introduction of exogenous full-length **trkB** into Ts16 neurons fully restored BDNF-dependent survival, whereas exogenous truncated **trkB** expression in normal, euploid neurons reproduced the Ts16 BDNF signaling failure. Thus, the failure of Ts16 neurons to respond to BDNF is caused by dysregulation of **trkB** isoform expression. Such a neurotrophin signaling defect could contribute to developmental and degenerative disorders of the nervous system.

...Abstract: trisomy 16 (Ts16) mouse, an animal model of Down syndrome. This failure is accompanied by **overexpression** of a truncated, kinase-deficient isoform (T1) of the BDNF receptor tyrosine receptor kinase B (**trkB**). Adenovirus-mediated introduction of exogenous full-length **trkB** into Ts16 neurons fully restored BDNF-dependent survival, whereas exogenous truncated **trkB** expression in normal, euploid neurons reproduced the Ts16 BDNF signaling failure. Thus, the failure of Ts16 neurons to respond to BDNF is caused by dysregulation of **trkB** isoform expression. Such a neurotrophin signaling defect could contribute to developmental and degenerative disorders of...
...Identifiers--TRUNCATED **TRKB** RECEPTORS; HIPPOCAMPAL-NEURONS; SIGNAL-TRANSDUCTION; SYNAPTIC PLASTICITY; NERVOUS-SYSTEM; DOWNS-SYNDROME; FULL-LENGTH; ALZHEIMERS-DISEASE...

16/3,K,AB/4 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05917758 Genuine Article#: XG646 Number of References: 81
Title: Trimethyltin exposure in the rat induces delayed changes in brain-derived neurotrophic factor, fos and heat shock protein 70 (ABSTRACT AVAILABLE)
Author(s): Andersson H (REPRINT) ; Wetmore C; Lindqvist E; Luthman J; Olson L
Corporate Source: KAROLINSKA INST,DEPT NEUROSCI/S-17177 STOCKHOLM//SWEDEN/ (REPRINT); ASTRA ARCUS AB,PRECLIN R&D, BEHAV & BIOCHEM PHARMACOL/SODERTALJE//SWEDEN/; UNIV MINNESOTA,/MINNEAPOLIS//MN/
Journal: NEUROTOXICOLOGY, 1997, V18, N1, P147-159
ISSN: 0161-813X Publication date: 19970000
Publisher: INTOX PRESS INC, PO BOX 24865, LITTLE ROCK, AR 72221
Language: English Document Type: ARTICLE
Abstract: Trimethyltin chloride (TMT) treatment in adult rats leads to limbic brain lesions that are detectable with classical neuropathological techniques 3 days after exposure. In particular, the hippocampal cells of the CA3c region are affected. The temporal and regional characteristics of TMT toxicity as reflected in changes of

activity-dependent factors were studied in adult male Sprague-Dawley rats using quantitative in situ hybridization and immunohistochemistry. No significant alterations in BDNF mRNA were defected in hippocampus and cerebral cortex 1 and 4 h after 8 mg TMT/kg. Three days after TMT, a significant increase in BDNF mRNA was detected in CA1, and increases in BDNF mRNA were also seen in cortical layers. An increase in BDNF hybridization signal was seen over scattered neurons within and outside CA3c at 3 days. Four h after 8 mg TMT/kg, BDNF immunoreactivity was reduced in the pyramidal cells of the CA3c and CA1 regions as well as in the dentate gyrus. No significant change in BDNF immunoreactivity was seen in hippocampus or cerebral cortex 3 days after TMT. BDNF interacts with the high-affinity receptor tyrosine kinase B (**trkB**). No immediate alteration in **trkB** mRNA was seen in hippocampus or cerebral cortex after 8 mg TMT/kg, while at 3 days **trkB** mRNA was significantly reduced in the CA3c pyramidal cell layer. No changes could be detected in neurotrophin-3 mRNA at either 1, 4 h or 3 days after TMT Three days after 8 mg TMT/kg, a major induction of hsp70 mRNA occurred in a subset of neurons in the CA3c region, concomitant with an increased expression of c-fos mRNA as well as Fos protein in the hilar region of hippocampus. Hence, an early and transient decrease in BDNF appears to occur after TMT exposure, which is succeeded at 3 days by increases in BDNF, c-fos and hsp 70 mRNAs, concomitant with a decrease in **trkB** mRNA in regions known to be vulnerable to TMT. These results demonstrate that TMT causes a delayed, spatially restricted increase in activity-dependent gene expression, making TMT-induced disturbances an interesting model of **neurodegenerative** events. (C) 1997 Inter Press, Inc.

...Abstract: cortex 3 days after TMT. BDNF interacts with the high-affinity receptor tyrosine kinase B (**trkB**). No immediate alteration in **trkB** mRNA was seen in hippocampus or cerebral cortex after 8 mg TMT/kg, while at 3 days **trkB** mRNA was significantly reduced in the CA3c pyramidal cell layer. No changes could be detected...

...by increases in BDNF, c-fos and hsp 70 mRNAs, concomitant with a decrease in **trkB** mRNA in regions known to be vulnerable to TMT. These results demonstrate that TMT causes...

...restricted increase in activity-dependent gene expression, making TMT-induced disturbances an interesting model of **neurodegenerative** events. (C) 1997 Inter Press, Inc.
...Identifiers--NERVE GROWTH-FACTOR; FACTOR MESSENGER-RNA; C-FOS; **DIFFERENTIAL** REGULATION; KAINIC ACID; INSITU HYBRIDIZATION; INCREASED EXPRESSION; HIPPOCAMPAL-NEURONS; MOLECULAR-CLONING; TYROSINE KINASE
...Research Fronts: 002 (NMDA RECEPTOR ANTAGONIST; GLUTAMATE-MEDIATED TOXICITY IN CULTURED RAT CORTICAL-NEURONS; GUINEA-PIG HIPPOCAMPUS; **DIFFERENTIAL** EXPRESSION)
95-1832 001 (RAT CEREBELLAR GRANULE NEURONS; BRAIN-DERIVED NEUROTROPHIC FACTOR; PC12 CELLS; TRKA...

16/3,K,AB/5 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03304918 Genuine Article#: NU579 Number of References: 73
Title: TARGET-DEPRIVED CNS NEURONS EXPRESS THE NGF GENE WHILE REACTIVE GLIA AROUND THEIR AXONAL TERMINALS CONTAIN LOW AND HIGH-AFFINITY NGF RECEPTORS (Abstract Available)
Author(s): JUNIER MP; SUZUKI F; ONTENIENTE B; PESCHANSKI M
Corporate Source: FAC MED CRETEIL,INSERM,CJF 9102,8 RUE GEN SARRAIL/F-94010 CRETEIL//FRANCE/
Journal: MOLECULAR BRAIN RESEARCH, 1994, V24, N1-4 (JUL), P247-260

ISSN: 0169-328X
Language: ENGLISH Document Type: ARTICLE
Abstract: Reactive gliosis is part of the response of central nervous system to injury and **neurodegeneration**. Cellular components of the reactive gliosis have the capability to synthesize neurotrophic factors, and thus are capable of affecting the fate of neuronal populations in the injured tissue. In this study, we explored the putative involvement of reactive glia-derived neurotrophins in sustaining the axonal projections of target-deprived neurons. Neuronal targets of the dorsal column nuclei neurons were suppressed through excitotoxic lesion of the ventrobasal complex of the rat thalamus (VB). Despite the development of reactive gliosis, neither up-regulation of NGF, nor BDNF or NT3 mRNA could be detected by solution hybridization in the lesioned site at all times tested. In contrast, expression of the LNGFR gene increased progressively up to 90 days post-lesion. Immunocytochemical studies localized the LNGFR protein in a subset of small cells with ramified processes resembling microglia at 7 and 20 days post-lesion. At longer times, double immunolabelling studies revealed that a substantial part of LNGFR-immunoreactive cells filling the area of neuronal loss were neither microglial cells nor astrocytes although presence of LNGFR in a subset of microglial cells could not be excluded. Previous ultrastructural studies of the kainate-lesioned VB suggest that these LNGFR-immunoreactive cells correspond to oligodendrocytes and/or Schwann cells. At 2 months post-lesion, when LNGFR expression was maximal, increased levels of trkA mRNA were detected in the lesioned site. Immunocytochemical studies revealed the presence of numerous trkA-immunoreactive astrocytes. **TrkB** mRNA, encoding the full-length high-affinity receptor for BDNF, remained undetectable by non-isotopic in situ hybridization. In contrast to the lack of neurotrophin gene expression by glial components of the lesioned VB, dorsal column nuclei neurons contained NGF mRNA as revealed by in situ hybridization studies at 10 days prior to enhanced LNGFR expression in the lesion - and 2 months post-lesion. In addition, the number and the staining intensity of NGF mRNA-positive neurons was increased in the target-deprived neurons, as compared with the contra-lateral nucleus projecting to intact targets. These results show that glial cells present in a reactive gliosis which develops in the kainic acid-lesioned thalamus, do not synthesize neurotrophins but instead produce high levels of both low- and high-affinity NGF receptors, LNGFR by Schwann cells/oligodendrocytes and possibly a subset of microglial cells, and trkA by reactive astrocytes. Presence of NGF mRNA in dorsal column nuclei neurons indicates that these neurons may be a source of ligand for these receptors. These results demonstrate that the different components required for NGF involvement in the 'cross-talk' between neurons and reactive gliosis are present in this experimental model: NGF in neurons, NGF receptors in reactive glial cells. They thus raise the possibility that target-deprived neurons and their glial environment have the potential to interact through the NGF/NGF receptors system.

Abstract: Reactive gliosis is part of the response of central nervous system to injury and **neurodegeneration**. Cellular components of the reactive gliosis have the capability to synthesize neurotrophic factors, and thus...

...detected in the lesioned site. Immunocytochemical studies revealed the presence of numerous trkA-immunoreactive astrocytes. **TrkB** mRNA, encoding the full-length high-affinity receptor for BDNF, remained undetectable by non-isotopic...
...Identifiers--FACTOR; GLUTAMIC-ACID DECARBOXYLASE; ADULT-RAT THALAMUS; MESSENGER-RNA; NEUROTROPHIC FACTOR; INSITU HYBRIDIZATION; SCHWANN-CELLS; **DIFFERENTIAL** REGULATION; CHOLINERGIC NEURONS; EXCITOTOXIC LESION
?

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YSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Sep W5
*File 155: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  55:Biosis Previews(R)  1993-2002/Sep W5
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removal, customized scheduling. See HELP ALERT.
  File  34:SciSearch(R) Cited Ref Sci  1990-2002/Oct W1
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  File 434:SciSearch(R) Cited Ref Sci  1974-1989/Dec
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  File 340:CLAIMS(R)/US Patent  1950-02/Oct 03
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 HELP NEWS340 & HELP ALERTS340 for search, display & Alert info.

      Set  Items  Description
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? s trkb
      S1    4273  TRKB
? s express?
      S2 2540838  EXPRESS?
? s s1 and s2
           4273  S1
        2540838  S2
      S3    3301  S1 AND S2
? s neurodegenerat?
      S4   38776  NEURODEGENERAT?
? s s3 and s4
           3301  S3
          38776  S4
      S5      76  S3 AND S4
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...examined 50 records  (50)
...completed examining records
      S6      41  RD (unique items)
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 6/3,K,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12993074   21845436   PMID: 11855816
   A discrete domain of the human TrkB receptor defines the binding
sites for BDNF and NT-4.
  Naylor Ruth L; Robertson Alan G S; Allen Shelley J; Sessions Richard B;
Clarke Anthony R; Mason Grant G F; Burston Judy J; Tyler Sue J; Wilcock
Gordon K; Dawbarn David
  University Research Centre for Neuroendocrinology (Care of the Elderly),
Bristol Royal Infirmary, Bristol, BS2 8HW, United Kingdom.
  Biochemical and biophysical research communications (United States)   Mar
1 2002,  291  (3)  p501-7,  ISSN 0006-291X   Journal Code: 0372516
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  TrkB is a member of the Trk family of tyrosine kinase receptors. In
vivo, the extracellular region of TrkB is known to bind, with high
affinity, the neurotrophin protein brain-derived neurotrophic factor (BDNF)
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and neurotrophin-4 (NT-4). We describe the **expression** and purification of the second Ig-like domain of human **TrkB** (TrkBIg(2)) and show, using surface plasmon resonance, that this domain is sufficient to bind BDNF and NT-4 with subnanomolar affinity. BDNF and NT-4 may have therapeutic implications for a variety of **neurodegenerative** diseases. The specificity of binding of the neurotrophins to their receptor **TrkB** is therefore of interest. We examine the specificity of TrkBIg(2) for all the neurotrophins, and use our molecular model of the BDNF-TrkBIg(2) complex to examine the residues involved in binding. It is hoped that the understanding of specific interactions will allow design of small molecule neurotrophin mimetics. 2002 Elsevier Science (USA).

A discrete domain of the human **TrkB** receptor defines the binding sites for BDNF and NT-4.

TrkB is a member of the Trk family of tyrosine kinase receptors. In vivo, the extracellular region of **TrkB** is known to bind, with high affinity, the neurotrophin protein brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4). We describe the **expression** and purification of the second Ig-like domain of human **TrkB** (TrkBIg(2)) and show, using surface plasmon resonance, that this domain is sufficient to bind...

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Descriptors: Brain-Derived Neurotrophic Factor--metabolism--ME; *Nerve Growth Factors--metabolism--ME; *Receptor, **trkB**--chemistry--CH; *Receptor, **trkB**--metabolism--ME...; Dichroism; Immunoglobulin Fragments--chemistry--CH; Kinetics; Models, Molecular; Molecular Sequence Data; Protein Structure, Tertiary; Receptor, **trkB**--isolation and purification--IP; Sequence Homology, Amino Acid; Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization...

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)

Chemical Name: Brain-Derived Neurotrophic Factor; Immunoglobulin Fragments; Nerve Growth Factors; neurotrophin 4; Receptor, **trkB**

6/3,K,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11354819 21437801 PMID: 11553687

The non-peptidyl fungal metabolite L-783,281 activates TRK neurotrophin receptors.

Wilkie N; Wingrove P B; Bilsland J G; Young L; Harper S J; Hefti F; Ellis S; Pollack S J

Department of Molecular Biology, Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre, Harlow, Essex, UK. neil wilkie@merck.com

Journal of neurochemistry (United States) Sep 2001, 78 (5) p1135-45, ISSN 0022-3042 Journal Code: 2985190R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Neurotrophin binding to the extracellular surface of the Trk family of tyrosine kinase receptors leads to the activation of multiple signalling cascades, culminating in neuroregenerative effects, including neuronal survival and neurite outgrowth. Since neurotrophins themselves are not ideal drug candidates due to their poor pharmacokinetic behaviour and bioavailability, small molecule neurotrophin mimetics may be beneficial in treating a number of **neurodegenerative** disorders. The present study demonstrates that L-783,281, a non-peptidyl fungal metabolite, is capable

of stimulating TrkA, B and C phosphorylation to various extents in CHO cells stably **expressing** human Trk receptors. L-783,281 also stimulated Trk phosphorylation in a number of rat and human primary neuronal cultures, whereas the highly similar compound, L-767,827, was without effect. Mechanistic studies utilizing transiently transfected PDGF/TrkA and TrkA/PDGF chimeras, demonstrated that L-783,281 is likely to interact with the intracellular domain of the TrkA receptor. Further investigations suggested that L-783,281 was nevertheless able to instigate receptor dimerization by binding in a non-covalent manner. Although the cytotoxicity of the compound was shown to preclude its effects in neuronal survival and neurite outgrowth assays, it is a prototype for a small molecule neurotrophin mimetic that activates Trk by interacting at a site different from the neurotrophin-binding site.

... behaviour and bioavailability, small molecule neurotrophin mimetics may be beneficial in treating a number of **neurodegenerative** disorders. The present study demonstrates that L-783,281, a non-peptidyl fungal metabolite, is capable of stimulating TrkA, B and C phosphorylation to various extents in CHO cells stably **expressing** human Trk receptors. L-783,281 also stimulated Trk phosphorylation in a number of rat ...

...; CY; Neurons--metabolism--ME; Phosphorylation; Rats; Receptor, trkA --genetics--GE; Receptor, trkA--metabolism--ME; Receptor, **trkB** --genetics--GE; Receptor, **trkB**--metabolism--ME; Receptor, trkC --genetics--GE; Receptor, trkC--metabolism--ME; Signal Transduction--drug effects--DE...

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 2.7.11.- (Receptor, trkA); EC 2.7.11.- (Receptor, trkC)

Chemical Name: Hypoglycemic Agents; Indoles; L 783281; Receptors, Nerve Growth Factor; Receptor, **trkB**; Receptor, trkA; Receptor, trkC

6/3,K,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10911548 20450877 PMID: 10993689

Expression of Trk isoforms in brain regions and in the striatum of patients with Alzheimer's disease.

Dubus P; Faucheux B; Boissiere F; Groppi A; Vital C; Vital A; Agid Y; Hirsch E C; Merlio J P

Laboratoire d'Histologie-Embryologie, EA 2406 Universite de Bordeaux 2, Bordeaux Cedex, 33076, France.

Experimental neurology (UNITED STATES) Oct 2000, 165 (2) p285-94, ISSN 0014-4886 Journal Code: 0370712

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The TrkAII tyrosine kinase receptor differs from the TrkAI isoform by an insertion of six amino acids in the extracellular domain. We used RT-PCR to determine their respective distribution in rat and human brain. Only trkAII transcripts were detected in 12 rat brain regions, while both trkAI and trkAII transcripts were detected in the cerebellum and pituitary gland. In human, both trkAI and trkAII transcripts were detected in the frontal, temporal, and occipital cortex and thalamus, while only trkAI transcripts were detected in the hippocampus and cerebellum. In the caudate and putamen, trkAII transcripts were exclusively detected. Thereafter, we studied the **expression** of TrkA isoforms in the striatum of five patients with Alzheimer's disease (AD), four patients with non-AD dementia, seven patients with Parkinson's disease, and six paired nondemented elderly control individuals. In controls and non-AD patients, a constant **expression** of trkAII transcripts was detected within all striatum parts. In AD patients, a heterogeneous decrease in trkAII **expression** was observed in the caudate, putamen, and ventral striatum, resulting

either in a drop of trkAII transcript levels or in a weak coamplification of trkAII and trkAI transcripts. The alteration of TrkAII gene **expression** paralleled those of choline acetyltransferase. Together with previous data, this suggests that the alteration of trk gene **expression** could contribute to a decrease in NGF binding sites and its protective effects on cholinergic neurons of AD patients. Copyright 2000 Academic Press.

Expression of Trk isoforms in brain regions and in the striatum of patients with Alzheimer's...
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... or in a weak coamplification of trkAII and trkAI transcripts. The alteration of TrkAII gene **expression** paralleled those of choline acetyltransferase. Together with previous data, this suggests that the alteration of trk gene **expression** could contribute to a decrease in NGF binding sites and its protective effects on cholinergic...
; Adult; Aged; Aged, 80 and over; Corpus Striatum--metabolism--ME; Middle Age; **Neurodegenerative** Diseases--metabolism--ME; Parkinson Disease --metabolism--ME; Protein Isoforms--metabolism--ME; Rats; Rats, Wistar; Receptor, **trkB**--metabolism--ME
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 2.7.11.- (Receptor, trkA)
Chemical Name: Protein Isoforms; Receptor, **trkB**; Receptor, trkA

6/3,K,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10711337 20256265 PMID: 10798407
Cortical degeneration in the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor **TrkB**.
Xu B; Zang K; Ruff N L; Zhang Y A; McConnell S K; Stryker M P; Reichardt L F
Department of Physiology, Howard Hughes Medical Institute, University of California, San Francisco 94143, USA.
Neuron (UNITED STATES) Apr 2000, 26 (1) p233-45, ISSN 0896-6273 Journal Code: 8809320
Contract/Grant No.: P01-16033; PHS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
To examine functions of **TrkB** in the adult CNS, **TrkB** has been removed from neurons **expressing** CaMKII, primarily pyramidal neurons, using Cre-mediated recombination. A floxed **trkB** allele was designed so that neurons lacking **TrkB express** tau-beta-galactosidase. Following **trkB** deletion in pyramidal cells, their dendritic arbors are altered, and cortical layers II/III and V are compressed, after which there is an apparent loss of mutant neurons **expressing** the transcription factor SCIP but not of those **expressing** Otx-1. Loss of neurons **expressing** SCIP requires deletion of **trkB** within affected neurons; reduction of neuronal ER81 **expression** does not, suggesting both direct and indirect effects of **TrkB** loss. Thus, **TrkB** is required for the maintenance of specific populations of cells

in the adult neocortex.

... the absence of neurotrophin signaling: dendritic retraction and neuronal loss after removal of the receptor **TrkB**.

To examine functions of **TrkB** in the adult CNS, **TrkB** has been removed from neurons **expressing** CaMKII, primarily pyramidal neurons, using Cre-mediated recombination. A floxed **trkB** allele was designed so that neurons lacking **TrkB express** tau-beta-galactosidase. Following **trkB** deletion in pyramidal cells, their dendritic arbors are altered, and cortical layers II/III and V are compressed, after which there is an apparent loss of mutant neurons **expressing** the transcription factor SCIP but not of those **expressing** Otx-1. Loss of neurons **expressing** SCIP requires deletion of **trkB** within affected neurons; reduction of neuronal ER81 **expression** does not, suggesting both direct and indirect effects of **TrkB** loss. Thus, **TrkB** is required for the maintenance of specific populations of cells in the adult neocortex.

Descriptors: Neocortex--metabolism--ME; *Neurons--metabolism--ME; *Pyramidal Cells--metabolism--ME; *Receptor, **trkB**--metabolism--ME; *beta-Galactosidase--metabolism--ME...; PA; Mice; Mice, Transgenic; Mutation--genetics--GE; Neocortex--pathology--PA; Nerve Growth Factors --metabolism--ME; **Neurodegenerative** Diseases--metabolism--ME; **Neurodegenerative** Diseases--pathology--PA; Neurons--pathology--PA; Receptor, **trkB**--genetics--GE; Transcription Factors--metabolism--ME

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**); EC 3.2.1.23 (beta-Galactosidase)

Chemical Name: DNA-Binding Proteins; ER81 protein; Nerve Growth Factors; Transcription Factors; Receptor, **trkB**; beta-Galactosidase

6/3,K,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10610139 20148565 PMID: 10683272

Upregulation of BDNF mRNA and **trkB** mRNA in the nigrostriatal system and in the lesion site following unilateral transection of the medial forebrain bundle.

Venero J L; Vizuete M L; Revuelta M; Vargas C; Cano J; Machado A

Departamento de Bioquimica, Bromatologia y Toxicologia, Seville, 41012, Spain.

Experimental neurology (UNITED STATES) Jan 2000, 161 (1) p38-48, ISSN 0014-4886 Journal Code: 0370712

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We have performed unilateral transection of the medial forebrain bundle (MFB) and studied BDNF mRNA and **trkB** mRNA levels at different postlesion times in the nigrostriatal system by means of in situ hybridization. BDNF mRNA levels were transiently induced in the substantia nigra pars compacta at 1 day postaxotomy. The disposition of BDNF mRNA **expressing** cells at this postlesion time in substantia nigra mimicked that of the dopaminergic neurons **expressing** the mRNA for the dopamine transporter. **TrkB** mRNA levels remained unaltered in the ventral mesencephalon at the different postlesion times examined-1 to 14 days. In contrast, **trkB** mRNA levels were significantly induced in the striatum at the longer postlesion time examined-14 days-when all **neurodegenerative** events are completed. It is becoming apparent that nigral BDNF mRNA levels are anterogradely transported to its target tissue in striatum. However, following axotomy, the lesion site represents a second potential target for BDNF action. Consequently, we also analyzed the pattern of mRNA **expression** for BDNF and **trkB** at the lesion site where dopaminergic axons are disconnected. There, we found notable inductions of both BDNF mRNA and **trkB** mRNA levels at 4 days

postaxotomy. BDNF mRNA **expressing** cells were confined at the site of axotomy, which coincided precisely to that showing induction of **trkB** mRNA. Altogether, our results anticipate promising trophic roles of BNDF in the injured nigrostriatal system. Copyright 2000 Academic Press.

Upregulation of BDNF mRNA and **trkB** mRNA in the nigrostriatal system and in the lesion site following unilateral transection of the...
... have performed unilateral transection of the medial forebrain bundle (MFB) and studied BDNF mRNA and **trkB** mRNA levels at different postlesion times in the nigrostriatal system by means of in situ...

... in the substantia nigra pars compacta at 1 day postaxotomy. The disposition of BDNF mRNA **expressing** cells at this postlesion time in substantia nigra mimicked that of the dopaminergic neurons **expressing** the mRNA for the dopamine transporter. **TrkB** mRNA levels remained unaltered in the ventral mesencephalon at the different postlesion times examined-1 to 14 days. In contrast, **trkB** mRNA levels were significantly induced in the striatum at the longer postlesion time examined-14 days-when all **neurodegenerative** events are completed. It is becoming apparent that nigral BDNF mRNA levels are anterogradely transported...

... a second potential target for BDNF action. Consequently, we also analyzed the pattern of mRNA **expression** for BDNF and **trkB** at the lesion site where dopaminergic axons are disconnected. There, we found notable inductions of both BDNF mRNA and **trkB** mRNA levels at 4 days postaxotomy. BDNF mRNA **expressing** cells were confined at the site of axotomy, which coincided precisely to that showing induction of **trkB** mRNA. Altogether, our results anticipate promising trophic roles of BNDF in the injured nigrostriatal system...
...Descriptors: Derived Neurotrophic Factor--genetics--GE; *Corpus Striatum--metabolism--ME; *Medial Forebrain Bundle--physiology--PH; *Receptor, **trkB**--genetics--GE; *Substantia Nigra--metabolism--ME...; Axotomy; Brain-Derived Neurotrophic Factor--metabolism--ME; Corpus Striatum --chemistry--CH; Dopamine--metabolism--ME; Gene **Expression** --physiology--PH; Image Processing, Computer-Assisted; In Situ Hybridization; Medial Forebrain Bundle--surgery--SU; RNA, Messenger --metabolism--ME; Rats; Rats, Wistar; Receptor, **trkB**--metabolism--ME; Substantia Nigra--chemistry--CH; Up-Regulation--physiology--PH
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)
Chemical Name: Brain-Derived Neurotrophic Factor; RNA, Messenger; Dopamine; Receptor, **trkB**

6/3,K,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10/8

10445523 99431463 PMID: 10502038
Absence of brain-derived neurotrophic factor and **trkB** receptor immunoreactivity in glia of Alzheimer's disease.
Soontornniyomkij V; Wang G; Pittman C A; Hamilton R L; Wiley C A; Achim C L
Department of Pathology (Neuropathology), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
Acta neuropathologica (GERMANY) Oct 1999, 98 (4) p345-8, ISSN 0001-6322 Journal Code: 0412041
Contract/Grant No.: NS35731; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Alterations in the neuronal **expression** of some neurotrophins have been shown in various **neurodegenerative** processes, particularly Alzheimer's disease (AD). Glia may up-regulate neurotrophins and their

high-affinity tyrosine kinase (trk) receptors in response to neural injury. In human immunodeficiency virus type 1 (HIV-1) encephalitis, activated microglia were shown to **express** brain-derived neurotrophic factor (BDNF), while reactive astrocytes **expressed trkB** receptor. This observation has suggested the existence of local neurotrophic regulation between different glial populations. To characterize the glial cellular distribution of BDNF and **trkB** receptor proteins in AD, we studied selected regions of postmortem brains from four AD and three age-matched control patients by double-immunofluorescence confocal microscopy. In both groups, BDNF immunoreactivity was distributed in neuronal perikarya and neuritic processes in the neocortex and hippocampus. No BDNF immunoreactivity was observed in microglia or astrocytes within and between senile plaques of AD. Catalytic **trkB** receptor immunoreactivity was present in neuronal perikarya in the neocortex and hippocampus. Reactive astrocytes and microglia were not immunoreactive for catalytic **trkB**. The absence of BDNF and **trkB** proteins in glia in AD patients is in contrast to the finding in patients with HIV-1 encephalitis. This difference suggests that glial **expression** of BDNF and **trkB** proteins may be characteristic of particular disease processes, rather than merely representing a stereotyped response to any type of neural injury.

Absence of brain-derived neurotrophic factor and **trkB** receptor immunoreactivity in glia of Alzheimer's disease.

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Descriptors: Alzheimer Disease--metabolism--ME; *Brain-Derived Neurotrophic Factor--metabolism--ME; *Neuroglia--metabolism--ME; *Receptor, **trkB**--metabolism--ME

Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)

Chemical Name: Brain-Derived Neurotrophic Factor; Receptor, **trkB**

6/3,K,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10351533 99332485 PMID: 10404406

Effects of aging and axotomy on the **expression** of neurotrophin receptors in primary sensory neurons.

Bergman E; Fundin B T; Ulfhake B

Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. esbjorn.bergman@neuro.ki.se

Journal of comparative neurology (UNITED STATES) Aug 2 1999, 410 (3) p368-86, ISSN 0021-9967 Journal Code: 0406041

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Aging is accompanied by declined sensory perception, paralleled by widespread dystrophic and degenerative changes in both central and peripheral sensory pathways. Several lines of evidence indicate that neurotrophic interactions are of importance for a maintained plasticity in the adult and aging nervous system, and that changes in the **expression** of neurotrophins and/or their receptors may underpin senile **neurodegeneration**. We have here examined the **expression** of neurotrophin receptor (p75NTR, trkA, **trkB**, and trkC) mRNA and protein in intact and axotomized primary sensory neurons of young adult (3 months) and aged (30 months) rats. To examine possible differences among primary sensory neuron populations, we have studied trigeminal ganglia (TG) as well as cervical and lumbar dorsal root ganglia (DRG). In intact aged rats, a decrease in trk (A/B/C) mRNA labeling densities and protein-like immunoreactivities was observed. The decrease was most pronounced in lumbar DRG. In contrast, a small, not statistically significant, increase of p75NTR **expression** was observed in aged DRG neuron profiles. After axotomy, a down-regulation of mRNA and protein levels was observed for all neurotrophin receptors (p75NTR, trkA, **trkB** and trkC) in both young adult and aged rats. Consistent with the higher **expression** levels of neurotrophin receptors in unlesioned young adult primary sensory neurons, the relative effect of axotomy was more pronounced in the young adult than aged rats. Although a decrease in mean cell profile cross-sectional areas was found during aging and after axotomy, the characteristic distribution of neurotrophin receptor **expression** in different populations of NRG neurons was conserved. The present findings suggest an attenuation of neurotrophic signaling in primary sensory neurons with advancing age and that the **expression** of p75NTR and trks is regulated differently during aging. A similar dissociation of p75NTR and trk regulation has previously been reported in other neuronal systems during aging, suggesting that there may be a common underlying mechanism. Decreased access to ligands, disturbed axon function and systemic changes in androgen/estrogen levels are discussed as inducing and/or contributing factors.

Effects of aging and axotomy on the **expression** of neurotrophin receptors in primary sensory neurons.

... a maintained plasticity in the adult and aging nervous system, and that changes in the **expression** of neurotrophins and/or their receptors may underpin senile **neurodegeneration** . We have here examined the **expression** of neurotrophin receptor (p75NTR, trkA, **trkB** , and trkC) mRNA and protein in intact and axotomized primary sensory neurons of young adult...

... most pronounced in lumbar DRG. In contrast, a small, not statistically significant, increase of p75NTR **expression** was observed in aged DRG neuron profiles. After axotomy, a down-regulation of mRNA and protein levels was observed for all neurotrophin receptors (p75NTR, trkA, **trkB** and trkC) in both young adult and aged rats. Consistent with the higher **expression** levels of neurotrophin receptors in unlesioned young adult primary sensory neurons, the relative effect of...

... sectional areas was found during aging and after axotomy, the characteristic distribution of neurotrophin receptor **expression** in different populations of NRG neurons was conserved. The present findings suggest an attenuation of neurotrophic signaling in primary sensory neurons with advancing age and that the **expression** of p75NTR and trks is regulated differently during aging. A similar dissociation of p75NTR and...

Descriptors: Aging--physiology--PH; *Ganglia, Spinal--metabolism--ME; *Gene **Expression** Regulation; *Neurons, Afferent--physiology--PH; *Proto-Oncogene Proteins--genetics--GE; *Receptor Protein-Tyrosine Kinases --genetics...

; Axotomy; Ganglia, Spinal--growth and development--GD; Gene **Expression** Regulation, Developmental; RNA, Messenger--genetics--GE; Rats; Rats, Sprague-Dawley; Receptor, Ciliary Neurotrophic Factor; Receptor ...

6/3,K,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10329445 99318250 PMID: 10391366

Alterations in BDNF and **trkB** mRNA levels in the cerebral cortex following experimental brain trauma in rats.

Hicks R R; Li C; Zhang L; Dhillon H S; Prasad M R; Seroogy K B
Division of Physical Therapy, University of Kentucky, Lexington 40536-0003, USA. rrhick00@pop.uky.edu

Journal of neurotrauma (UNITED STATES) Jun 1999, 16 (6) p501-10, ISSN 0897-7151 Journal Code: 8811626
Contract/Grant No.: NS31816; NS; NINDS; NS35164; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Recent studies have suggested that brain-derived neurotrophic factor (BNDF) and its receptor, **trkB**, may provide neuroprotection following injury to the central nervous system. Conversely, other studies have implicated BDNF as a contributing factor to **neurodegenerative** events that occur following injury. In order to further investigate the role of BDNF in neuroprotection, we subjected adult rats to a lateral fluid percussion (FP) injury of moderate severity (2.0-2.1 atm) or sham injury. After survival periods of 1, 3, 6, 24, or 72 h, the brains were processed for the in situ hybridization localization of BDNF and **trkB** mRNAs using 35S-labeled cRNA probes. Hybridization levels were compared between injured and sham animals for regions of the cortex that were located within, adjacent to, and remote from the site of the cortical contusion. BDNF mRNA levels were significantly decreased in the injured cortex at 72 h, increased in adjacent cortical areas at 3 h, and increased bilaterally in the piriform cortex from 3 to 24 h post-FP injury. **Expression** of **trkB** mRNA was significantly decreased at all postinjury time-points in the injured cortex and at 24 h in the adjacent cortex. These results demonstrate that, following lateral FP injury, BDNF and **trkB** mRNA levels are decreased in cortical regions that contain degenerating neurons, generally unchanged in adjacent regions, and increased in remote areas. Thus, injury-induced decreases in the **expression** of BDNF and **trkB** may confer vulnerability to neurons within the cortical contusion.

Alterations in BDNF and **trkB** mRNA levels in the cerebral cortex following experimental brain trauma in rats.
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lateral FP injury, BDNF and **trkB** mRNA levels are decreased in cortical regions that contain degenerating neurons, generally unchanged in adjacent regions, and increased in remote areas. Thus, injury-induced decreases in the **expression** of BDNF and **trkB** may confer vulnerability to neurons within the cortical contusion.
...Descriptors: Brain-Derived Neurotrophic Factor--metabolism--ME; *Cerebral Cortex--metabolism--ME; *RNA, Messenger--metabolism--ME; *Receptor, **trkB**--metabolism--ME; Autoradiography; Cerebral Cortex --injuries--IN; Disease Models, Animal; Gene **Expression** Regulation; In Situ Hybridization; Rats; Rats, Sprague-Dawley; Time Factors
Enzyme No.: EC 2.6.11.- (Receptor, **trkB**)
Chemical Name: Brain-Derived Neurotrophic Factor; RNA, Messenger; Receptor, **trkB**

6/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10291206 99280570 PMID: 10350634
Expression of p75(NTR), **trkB** and trkC in nonmanipulated and axotomized motoneurons of aged rats.
Johnson H; Hokfelt T; Ulfhake B
Department of Neuroscience, Karolinska Institutet, Division of Neuroanatomy and Neuronal Plasticity, S-171 77, Stockholm, Sweden. hans.johnson@neuro.ki.se
Brain research. Molecular brain research (NETHERLANDS) May 21 1999, 69 (1) p21-34, ISSN 0169-328X Journal Code: 8908640
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several lines of evidence indicate that adult neurons remain dependent on neurotrophins and that changes in tissue **expression** of neurotrophins and/or their receptors may play a role in senile **neurodegeneration**. We have studied the **expression** of p75NTR, **trkB** and trkC, respectively, in lumbar motoneurons of young adult (2-3 months) and aged (30 months) rats subjected to sciatic transection using in situ hybridization and immunohistochemistry. Nonmanipulated age-matched animals were processed in parallel. In nonmanipulated aged rats, high levels of p75NTR could be seen in a number of motoneurons (10-15%), while in young adult animals no p75NTR could be detected. Seven days following sciatic axotomy, a conspicuous ipsilateral upregulation p75NTR was observed in young adult rats. Also in aged rats there was a marked ipsilateral increase in number of p75NTR **expressing** neurons (approximately 100%). In comparison to young adult rats, aged rats showed a decreased **expression** of both **trkB** (5/6 animals) and trkC (6/6 animals). Furthermore, in response to sciatic transection, 3 out of 5 aged rats did not show an increased **expression** of **trkB**. In aged rats, axotomy did not induce any significant change in trkC **expression**. In the young adult rats, we recorded a side-to-side effect with lower values ipsilaterally, however, it cannot be excluded that this difference was caused by an upregulation in the contralateral motoneurons. Oligonucleotide probes against BDNF and NT3 mRNA showed only very few faintly positive neurons in both age groups. Our results indicate that the pattern of regulatory changes of NT receptors in response to axotomy is different in aged and young adult rats. The lack of covariation between p75NTR and **trkB** and trkC regulation in aged rats indicates a changed role for p75NTR in senescent motoneurons. Copyright 1999 Elsevier Science B.V.

Expression of p75(NTR), **trkB** and trkC in nonmanipulated and axotomized motoneurons of aged rats.
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; Axotomy; Behavior, Animal--physiology--PH; Brain-Derived Neurotrophic Factor--genetics--GE; Gene **Expression**--physiology--PH; Immunohistoche mistry; In Situ Hybridization; Nerve Growth Factors--genetics--GE; Neuroprotective Agents--analysis--AN...

6/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10144314 99105102 PMID: 9888155
Expression of brain-derived neurotrophic factor protein in activated microglia of human immunodeficiency virus type 1 encephalitis.
Soontornniyomkij V; Wang G; Pittman C A; Wiley C A; Achim C L
Department of Pathology (Neuropathology), University of Pittsburgh School of Medicine, Pennsylvania, USA.
Neuropathology and applied neurobiology (ENGLAND) Dec 1998, 24 (6) p453-60, ISSN 0305-1846 Journal Code: 7609829
Contract/Grant No.: NS35731; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The role of neurotrophic factors and their therapeutic potential have been investigated in various **neurodegenerative** disorders. In **neurodegeneration** associated with human immunodeficiency virus (HIV) infection, neuronal function and survival may be affected by abnormal neurotrophic regulation involving HIV-infected microglia and reactive astrocytes. To characterize the cellular localization of brain-derived neurotrophic factor (BDNF) and its high-affinity tyrosine kinase receptor, **trkB** , proteins in HIV-1 encephalitis, we examined post-mortem brains from patients with acquired immunodeficiency syndrome and brains from non-HIV-infected controls. Using double immunofluorescent confocal microscopy, we found that BDNF immunoreactivity was distributed in neocortical neuronal perikarya and neuritic processes, while in the striatum only neurites were BDNF-immunoreactive. Additionally, the striatum with HIV infection was characterized by BDNF immunoreactivity in infiltrating activated microglia/macrophages and multinucleated giant cells. Catalytic **trkB** receptor immunoreactivity was observed in neuronal perikarya in the neocortex and striatum, as well as in reactive astrocytes within HIV-infected regions. Our findings suggest that **expression** of BDNF by activated microglia in HIV-1 encephalitis may affect neuronal survival and astroglial response through corresponding **trkB** receptors.

Expression of brain-derived neurotrophic factor protein in activated microglia of human immunodeficiency virus type 1...
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... cellular localization of brain-derived neurotrophic factor (BDNF) and its high-affinity tyrosine kinase receptor, **trkB**, proteins in HIV-1 encephalitis, we examined post-mortem brains from patients with acquired immunodeficiency...

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6/3,K,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10/8

09938718 98355468 PMID: 9692719

trkB messenger RNA **expression** in normal human brain and in the substantia nigra of parkinsonian patients: an in situ hybridization study.

Benisty S; Boissiere F; Faucheux B; Agid Y; Hirsch E C
INSERM U 289, Hopital de la Salpetriere, Paris, France.

Neuroscience (UNITED STATES) Oct 1998, 86 (3) p813-26, ISSN 0306-4522 Journal Code: 7605074
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

trkB is a high-affinity receptor for brain-derived neurotrophic factor, a neurotrophin acting on numerous cells, including dopaminergic neurons. Yet, little is known of its **expression** in the human brain. We report an in situ hybridization analysis of **trkB** messenger RNA, encoding the catalytic form of the receptor, in the human brain post mortem. Its **expression** was found to be widespread but heterogeneous among all the cerebral structures studied, the highest level being found in the cerebral cortex and the cerebellum. A strong but less intense staining was observed in the striatum, nucleus basalis of Meynert, hippocampus, tegmental pedonculopontinus nucleus and substantia nigra pars compacta. Combined immunohistochemistry for tyrosine hydroxylase and in situ hybridization for **trkB** messenger RNA showed that within the substantia nigra pars compacta a major proportion of dopaminergic neurons **expressed trkB** messenger RNA. Furthermore, we compared **trkB** messenger RNA **expression** in the mesencephalon of six control subjects and five patients with Parkinson's disease, a **neurodegenerative** disorder characterized by a severe loss of dopaminergic neurons. Despite the fact that the number of **trkB** messenger RNA-containing neurons was dramatically reduced in the substantia nigra pars compacta and ventral tegmental area of patients with Parkinson's disease, the level of **trkB** messenger RNA was unchanged in the remaining neurons in diseased brains. These results suggests that **trkB** is not involved in the process of neuronal death in Parkinson's disease. Furthermore, **expression** of brain-derived neurotrophic factor high-affinity receptor in patients could allow this neurotrophin to be used to prevent degeneration of surviving neurons at early stages of the disease.

trkB messenger RNA **expression** in normal human brain and in the substantia nigra of parkinsonian patients: an in situ...

trkB is a high-affinity receptor for brain-derived neurotrophic factor, a neurotrophin acting on numerous cells, including dopaminergic

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10/Y

6/3,K,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09787248 98206360 PMID: 9546284
BDNF up-regulates **TrkB** protein and prevents the death of CA1 neurons following transient forebrain ischemia.
Ferrer I; Ballabriga J; Marti E; Perez E; Alberch J; Arenas E
Unitat de Neuropatologia, Servei d'Anatomia Patoligica, Hospital Princeps d'Espanya, Spain.
Brain pathology (Zurich, Switzerland) (SWITZERLAND) Apr 1998, 8 (2) p253-61, ISSN 1015-6305 Journal Code: 9216781
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The neurotrophin family of growth factors, which includes Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT3) and Neurotrophin-4/5 (NT4/5) bind and activate specific tyrosine kinase (Trk) receptors to promote cell survival and growth of different cell populations. For these reasons, growing attention has been paid to the use of neurotrophins as therapeutic agents in **neurodegeneration**, and to the regulation of the **expression** of their specific receptors by the ligands. BDNF **expression**, as revealed by immunohistochemistry, is found in the pre-subiculum, CA1, CA3, and dentate gyrus of the hippocampus. Strong **TrkB** immunoreactivity is present in most CA3 neurons but only in scattered neurons of the CA1 area. Weak **TrkB** immunoreactivity is found in the granule cell layer of the dentate gyrus. Unilateral grafting of BDNF-transfected fibroblasts into the hippocampus resulted in a marked increase in the intensity of the immunoreaction and in the number of **TrkB** -immunoreactive neurons in the granule cell layer of the dentate gyrus, pre-subiculum and CA1 area in the vicinity of the graft. No similar effects were produced after the injection of control mock-transfected fibroblasts. Delayed cell death in the CA1 area was produced following 5 min of forebrain ischemia in the gerbil. The majority of living cells in the CA1 area at the fourth day were BDNF/**TrkB** immunoreactive. Unilateral grafting of control mock-transfected or BDNF fibroblasts two days before ischemia resulted in a moderate non-specific protection of **TrkB**-negative, but not **TrkB**-positive cells, in the CA1 area of the grafted side. This finding is in line with a vascular and glial reaction, as revealed, by immunohistochemistry using astroglial and microglial cell markers. This astroglial response was higher in the grafted

side than in the contralateral side in ischemic gerbils, but no differences were seen between BDNF-producing and non-BDNF-producing grafts. However, grafting of BDNF-producing fibroblasts two days before ischemia significantly and specifically prevented nerve cells from dying in the CA1 area of the ipsilateral hippocampus. Cell survival was associated with increased **TrkB** immunoreactivity as the majority of living cells were **TrkB** immunoreactive. Thus, our results show that BDNF is able to up-regulate the **expression** of **TrkB** in control and pathological states, and that BDNF prevention of neuronal death following transient forebrain ischemia is associated with increased **expression** of its specific receptor.

BDNF up-regulates **TrkB** protein and prevents the death of CA1 neurons following transient forebrain ischemia.
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6/3,K,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10/V

09754041 98167361 PMID: 9507943
Decreased trkA neurotrophin receptor **expression** in the parietal cortex of patients with Alzheimer's disease.
Hock C; Heese K; Muller-Spahn F; Hulette C; Rosenberg C; Otten U
Department of Psychiatry (PUK), University of Basel, Switzerland. chock@datacomm.ch
Neuroscience letters (IRELAND) Jan 30 1998, 241 (2-3) p151-4, ISSN 0304-3940 Journal Code: 7600130
Contract/Grant No.: P50-AG05128; AG; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The cholinergic neurons of the basal forebrain system are sensitive to nerve growth factor (NGF), a member of the neurotrophin gene family. Since the cholinergic system is affected early in the course of Alzheimer's disease (AD), it was hypothesized that a deficit in NGF, e.g. reduced neurotrophin uptake by specific receptors, may play a role in neuronal cell

death in AD. We quantitated mRNA levels of neurotrophins (NGF, BDNF, NT-3, NT-4/5) and their receptors (trkA, **trkB**, trkC, p75) in AD postmortem parietal cortex (n = 16) and cerebellum (n = 11). We applied highly sensitive reverse transcription-polymerase chain reaction (RT-PCR) in rapid autopsy derived brain tissue (mean postmortem delay 147+/-96 min., n = 53) to minimize postmortem mRNA variations. In the AD parietal cortex trkA mRNA levels were more than two times lower as compared to controls (n = 16, mean+/-SEM 0.26+/-0.07 units/S12, range, 0-1.78, and n = 11, 0.59+/-0.10 units/S12, range, 0.17-1.10, respectively, P = 0.015). TrkA mRNA levels did not appear to be altered in the AD cerebellum as compared to normal human cerebellum. NGF, BDNF, NT-3, NT-4/5, as well as **trkB**, trkC and p75 mRNA levels were unchanged in AD parietal cortex and cerebellum as compared to controls. This finding suggests that a reduced **expression** of the trkA receptor may contribute to impaired NGF-trkA signalling and a reduced transport of NGF in cholinergic neurons. These results reveal a central specific role of the high affinity NGF receptor during **neurodegeneration** in AD.

Decreased trkA neurotrophin receptor **expression** in the parietal cortex of patients with Alzheimer's disease.
... mRNA levels of neurotrophins (NGF, BDNF, NT-3, NT-4/5) and their receptors (trkA, **trkB**, trkC, p75) in AD postmortem parietal cortex (n = 16) and cerebellum (n = 11). We applied...

...compared to normal human cerebellum. NGF, BDNF, NT-3, NT-4/5, as well as **trkB** , trkC and p75 mRNA levels were unchanged in AD parietal cortex and cerebellum as compared to controls. This finding suggests that a reduced **expression** of the trkA receptor may contribute to impaired NGF-trkA signalling and a reduced transport...

... neurons. These results reveal a central specific role of the high affinity NGF receptor during **neurodegeneration** in AD.

6/3,K,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09610259 98030900 PMID: 9364325
Cell death of adult pyramidal CA1 neurons after intraventricular injection of a novel peptide derived from trkA.
Kadari A; Windisch J M; Ebendal T; Schneider R; Humpel C
Department of Psychiatry, University of Innsbruck, Austria.
Journal of neuroscience research (UNITED STATES) Nov 1 1997, 50 (3) p402-12, ISSN 0360-4012 Journal Code: 7600111
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Members of the nerve growth factor (NGF) family of neurotrophins bind to the second leucine-rich motif (LRM2) within the extracellular domains of their respective receptors (trkA, **trkB**, trkC). Small LRM2 peptides have been recently demonstrated to selectively bind the neurotrophins revealing similar complex binding characteristics as full-length receptors. We extend our recent findings, showing that the peptides (A and C) do not block nerve fiber outgrowth through high affinity trk receptors in a ganglia bioassay. Since the highest concentration of neurotrophins [NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3)] is found in the hippocampus, the peptides were injected into the 3rd ventricle of anesthetized adult rats. The (NGF binding) LRM2-A peptide, but not the (BDNF binding) LRM2-B or the (NT-3 binding) LRM2-C peptides, caused severe apoptotic **neurodegeneration** of hippocampal pyramidal CA1 neurons as revealed by cresyl violet staining and the TUNEL reaction. The degeneration was protected by intrahippocampal injection of NGF-beta and by the non-N-methyl-D-aspartate (NMDA) antagonist CNQX (6-cyano-7-nitroquinoxaline

-2,3-dione), indicating a glutamatergic mechanism. In situ hybridization revealed that pyramidal CA1 neurons did not **express** trkA and p75 receptor mRNA in sham and LRM2-A-lesioned animals. It is concluded that the LRM2-A peptide represents a novel peptide with properties to induce apoptotic cell death of pyramidal CA1 neurons and may be useful as an experimental agent.

... the second leucine-rich motif (LRM2) within the extracellular domains of their respective receptors (trkA, **trkB**, trkC). Small LRM2 peptides have been recently demonstrated to selectively bind the neurotrophins revealing similar...

... BDNF binding) LRM2-B or the (NT-3 binding) LRM2-C peptides, caused severe apoptotic **neurodegeneration** of hippocampal pyramidal CA1 neurons as revealed by cresyl violet staining and the TUNEL reaction... ... dione), indicating a glutamatergic mechanism. In situ hybridization revealed that pyramidal CA1 neurons did not **express** trkA and p75 receptor mRNA in sham and LRM2-A-lesioned animals. It is concluded...

6/3,K,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09458391 97358977 PMID: 9215997
Trimethyltin exposure in the rat induces delayed changes in brain-derived neurotrophic factor, fos and heat shock protein 70.
Andersson H; Wetmore C; Lindqvist E; Luthman J; Olson L
Department of Neuroscience, Karolinska Institute, Stockholm, Sweden.
Neurotoxicology (UNITED STATES) 1997, 18 (1) p147-59, ISSN 0161-813X Journal Code: 7905589
Contract/Grant No.: AG04418; AG; NIA; NS09199; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Trimethyltin chloride (TMT) treatment in adult rats leads to limbic brain lesions that are detectable with classical neuropathological techniques 3 days after exposure. In particular, the hippocampal cells of the CA3c region are affected. The temporal and regional characteristics of TMT toxicity as reflected in changes of activity-dependent factors were studied in adult male Sprague-Dawley rats using quantitative in situ hybridization and immunohistochemistry. No significant alterations in the BDNF mRNA were detected in hippocampus and cerebral cortex 1 and 4 h after 8 mg TMT/kg. Three days after TMT, a significant increase in BDNF mRNA was detected in CA1, and increases in BDNF mRNA were also seen in cortical layers. An increase in BDNF hybridization signal was seen over scattered neurons within and outside CA3c at 3 days. Four h after 8 mg TMT/kg, BDNF immunoreactivity was reduced in the pyramidal cells of the CA3c and CA1 regions as well as in the dentate gyrus. No significant change in BDNF immunoreactivity was seen in hippocampus or cerebral cortex 3 days after TMT. BDNF interacts with the high-affinity receptor tyrosine kinase B (**trkB**). No immediate alteration in **trkB** mRNA was seen in hippocampus or cerebral cortex after 8 mg TMT/kg, while at 3 days **trkB** mRNA was significantly reduced in the CA3c pyramidal cell layer. No changes could be detected in neurotrophin-3 mRNA at either 1, 4 h or 3 days after TMT. Three days after 8 mg TMT/kg, a major induction of hsp70 mRNA occurred in a subset of neurons in the CA3c region, concomitant with an increased **expression** of c-fos mRNA as well as Fos protein in the hilar region of hippocampus. Hence, an early and transient decrease in BDNF appears to occur after TMT exposure, which is succeeded at 3 days by increases in BDNF, c-fos and hsp 70 mRNAs, concomitant with a decrease in **trkB** mRNA in regions known to be vulnerable to TMT. These results demonstrate that TMT causes a delayed, spatially restricted increase in activity-dependent gene **expression**, making TMT-induced disturbances

an interesting model of **neurodegenerative** events.
... cortex 3 days after TMT. BDNF interacts with the high-affinity receptor tyrosine kinase B (**trkB**). No immediate alteration in **trkB** mRNA was seen in hippocampus or cerebral cortex after 8 mg TMT/kg, while at 3 days **trkB** mRNA was significantly reduced in the CA3c pyramidal cell layer. No changes could be detected...

... mRNA occurred in a subset of neurons in the CA3c region, concomitant with an increased **expression** of c-fos mRNA as well as Fos protein in the hilar region of hippocampus...

... by increases in BDNF, c-fos and hsp 70 mRNAs, concomitant with a decrease in **trkB** mRNA in regions known to be vulnerable to TMT. These results demonstrate that TMT causes a delayed, spatially restricted increase in activity-dependent gene **expression**, making TMT-induced disturbances an interesting model of **neurodegenerative** events.

6/3,K,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09037089 96373716 PMID: 8780007
Suppression of p140trkA does not abolish nerve growth factor-mediated rescue of serum-free PC12 cells.
Taglialatela G; Hibbert C J; Hutton L A; Werrbach-Perez K; Perez-Polo J R
Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch at Galveston 77555-0652, USA.
Journal of neurochemistry (UNITED STATES) May 1996, 66 (5) p1826-35, ISSN 0022-3042 Journal Code: 2985190R
Contract/Grant No.: NS18708; NS; NINDS; P01AG10514; AG; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Programmed cell death, the intrinsic form of apoptosis, plays an integral role in those **neurodegenerative** events associated with age-related neuropathology. Neurotrophins (NTs), such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and NT-3, are required for survival of certain neurons, and thus their clinical use to counteract age- and pathology-associated **neurodegeneration** has been suggested, although mechanistic descriptions for NT cell rescue from apoptosis are not definitive. Here we attempted to isolate the individual actions of high-affinity tyrosine kinase (Trk) receptors and p75NGFR, the common low-affinity NT receptor, in NT rescue of apoptotic PC12 cells. Our results showed that whereas inhibiting Trk receptor phosphorylation abolishes NGF rescue of serum-deprived PC12 cells from apoptosis, TrkA suppression with antisense oligonucleotides did not. Also, although BDNF did not rescue naive serumless PC12 cells, which lack the BDNF-specific **TrkB** receptor, it significantly increased survival of TrkA-suppressed serum-starved PC12 cells. These data confirm the hypothesis that binding of any NT to Trk-free p75NGFR-bearing cells blocks apoptosis but also suggest that if Trk receptors are **expressed**, prohibiting Trk phosphorylation also blocks NT-mediated rescue from apoptosis.

Programmed cell death, the intrinsic form of apoptosis, plays an integral role in those **neurodegenerative** events associated with age-related neuropathology. Neurotrophins (NTs), such as nerve growth factor (NGF), brain...

... survival of certain neurons, and thus their clinical use to counteract age- and pathology-associated **neurodegeneration** has been suggested, although mechanistic descriptions for NT cell rescue from apoptosis are not definitive...
... Also, although BDNF did not rescue naive serumless PC12 cells, which

lack the BDNF-specific **TrkB** receptor, it significantly increased survival of TrkA-suppressed serum-starved PC12 cells. These data confirm...

...Trk-free p75NGFR-bearing cells blocks apoptosis but also suggest that if Trk receptors are **expressed** , prohibiting Trk phosphorylation also blocks NT-mediated rescue from apoptosis.

6/3,K,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10/8

08918818 96254913 PMID: 8963440
Decreased **expression** of **TrkB** and TrkC mRNAs in spinal motoneurons of aged rats.
Johnson H; Hokfelt T; Ulfhake B
Department of Neuroscience, Karolinska Institute, Stockholm, Sweden.
European journal of neuroscience (ENGLAND) Mar 1996, 8 (3) p494-9, ISSN 0953-816X Journal Code: 8918110
Contract/Grant No.: AG 10491; AG; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several studies have indicated that a decrease in availability and/or responsiveness to neurotrophin(s) may be of importance in ageing and disease-related **neurodegeneration** . Using in situ hybridization we have studied the mRNA **expression** of the full-length neurotrophin receptors **TrkB** and TrkC in spinal cord motoneurons of aged rats (30 months old) with symptoms of hindlimb incapacity and in young adult rats (2-3 months old). The labelling intensity for **TrkB** of the individual cell profile was decreased by 25% ($P < 0.001$) in both the cervical and lumbar motor nuclei of aged rats. In thoracic motoneurons of aged and young adult rats the difference in **expression** of **TrkB** mRNA was smaller (down by 15%; $P < 0.05$). The labelling for TrkC mRNA was much weaker than that for **TrkB** in both aged and young adult rats, but TrkC mRNA **expression** also seemed to decrease. Comparison of the different motor nuclei along the spinal cord axis revealed that the motoneurons of the L6/S1 nuclei showed the strongest hybridization signal for the two Trk receptors in both aged and young adult rats. The possibility that a decrease in **TrkB** mRNA may contribute to age-related motor disturbances is discussed.

Decreased **expression** of **TrkB** and TrkC mRNAs in spinal motoneurons of aged rats.
... and/or responsiveness to neurotrophin(s) may be of importance in ageing and disease-related **neurodegeneration** . Using in situ hybridization we have studied the mRNA **expression** of the full-length neurotrophin receptors **TrkB** and TrkC in spinal cord motoneurons of aged rats (30 months old) with symptoms of hindlimb incapacity and in young adult rats (2-3 months old). The labelling intensity for **TrkB** of the individual cell profile was decreased by 25% ($P < 0.001$) in both the...

... of aged rats. In thoracic motoneurons of aged and young adult rats the difference in **expression** of **TrkB** mRNA was smaller (down by 15%; $P < 0.05$). The labelling for TrkC mRNA was much weaker than that for **TrkB** in both aged and young adult rats, but TrkC mRNA **expression** also seemed to decrease. Comparison of the different motor nuclei along the spinal cord axis...

... Trk receptors in both aged and young adult rats. The possibility that a decrease in **TrkB** mRNA may contribute to age-related motor disturbances is discussed.

6/3,K,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08467184 95241600 PMID: 7724649
Neurotrophins: a family of proteins supporting the survival of neurons.
Barde Y A
Department of Neurobiochemistry, Max-Planck Institute for Psychiatry, Planegg-Murtinsred, Germany.
Progress in clinical and biological research (UNITED STATES) 1994, 390 p45-56, ISSN 0361-7742 Journal Code: 7605701
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
NGF, BDNF, NT-3, and NT-4/5 are all members of a structurally related family of molecules that function to prevent the death of embryonic neurons during development. The presence of these molecules in the targets of innervating neurons is likely to explain at least in part why many neurons depend on their target tissues for survival. A small family of related membrane proteins with a ligand-activable tyrosine kinase and **expressed** in the nervous system represents a significant part of the structural basis explaining how neurons discriminate between the neurotrophins and transduce the consequence of neurotrophin binding. Thus, much structural information has been obtained that contributes to better understand some important aspects of vertebrate neurogenesis, particularly those related to selective cell survival in a very diverse cellular system like the nervous system. Future studies will have to explain how the role of these molecules has to be understood in the context of the characteristic features of the nervous system, in particular neurotransmission and electrical activity. Finally, while the role of neurotrophins has been discussed here in the context of the developing nervous system, it will be important to understand what functions these molecules might play in the central nervous system. For example, neurotrophins might function as long term mediators of changes in cellular shapes under the influence of electrical activity, as well as in pathological situations when axonal elongation is needed to restore connections, or to maintain the well-being of neurons that are eliminated during the course of **neurodegenerative** diseases.

... survival. A small family of related membrane proteins with a ligand-activable tyrosine kinase and **expressed** in the nervous system represents a significant part of the structural basis explaining how neurons...

... or to maintain the well-being of neurons that are eliminated during the course of **neurodegenerative** diseases.
Gene Symbol: trk; **trkB**; trkC

6/3,K,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08308931 95057989 PMID: 7968364
Target-deprived CNS neurons **express** the NGF gene while reactive glia around their axonal terminals contain low and high affinity NGF receptors.
Junier M P; Suzuki F; Onteniente B; Peschanski M
INSERM CJF 91-02, Faculte Medecine, Creteil, France.
Brain research. Molecular brain research (NETHERLANDS) Jul 1994, 24 (1-4) p247-60, ISSN 0169-328X Journal Code: 8908640
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Reactive gliosis is part of the response of central nervous system to injury and **neurodegeneration** . Cellular components of the reactive gliosis have the capability to synthesize neurotrophic factors, and thus are capable of affecting the fate of neuronal populations in the injured tissue. In this study, we explored the putative involvement of reactive glia-derived neurotrophins in sustaining the axonal projections of target-deprived neurons. Neuronal targets of the dorsal column nuclei neurons were suppressed through excitotoxic lesion of the ventrobasal complex of the rat thalamus (VB). Despite the development of reactive gliosis, neither up-regulation of NGF, nor BDNF or NT3 mRNA could be detected by solution hybridization in the lesioned site at all times tested. In contrast, **expression** of the LNGFR gene increased progressively up to 90 days post-lesion. Immunocytochemical studies localized the LNGFR protein in a subset of small cells with ramified processes resembling microglia at 7 and 20 days post-lesion. At longer times, double immunolabelling studies revealed that a substantial part of LNGFR-immunoreactive cells filling the area of neuronal loss were neither microglial cells nor astrocytes although presence of LNGFR in a subset of microglial cells could not be excluded. Previous ultrastructural studies of the kainate-lesioned VB suggest that these LNGFR-immunoreactive cells correspond to oligodendrocytes and/or Schwann cells. At 2 months post-lesion, when LNGFR **expression** was maximal, increased levels of trkA mRNA were detected in the lesioned site. Immunocytochemical studies revealed the presence of numerous trkA-immunoreactive astrocytes. **TrkB** mRNA, encoding the full-length high-affinity receptor for BDNF, remained undetectable by non-isotopic in situ hybridization. In contrast to the lack of neurotrophin gene **expression** by glial components of the lesioned VB, dorsal column nuclei neurons contained NGF mRNA as revealed by in situ hybridization studies at 10 days--prior to enhanced LNGFR **expression** in the lesion--and 2 months post-lesion. In addition, the number and the staining intensity of NGF mRNA-positive neurons was increased in the target-deprived neurons, as compared with the contra-lateral nucleus projecting to intact targets. These results show that glial cells present in a reactive gliosis which develops in the kainic acid-lesioned thalamus, do not synthesize neurotrophins but instead produce high levels of both low- and high-affinity NGF receptors, LNGFR by Schwann cells/oligodendrocytes and possibly a subset of microglial cells, and trkA by reactive astrocytes.(ABSTRACT TRUNCATED AT 400 WORDS)

Target-deprived CNS neurons **express** the NGF gene while reactive glia around their axonal terminals contain low and high affinity...
Reactive gliosis is part of the response of central nervous system to injury and **neurodegeneration** . Cellular components of the reactive gliosis have the capability to synthesize neurotrophic factors, and thus...

... be detected by solution hybridization in the lesioned site at all times tested. In contrast, **expression** of the LNGFR gene increased progressively up to 90 days post-lesion. Immunocytochemical studies localized...

... cells correspond to oligodendrocytes and/or Schwann cells. At 2 months post-lesion, when LNGFR **expression** was maximal, increased levels of trkA mRNA were detected in the lesioned site. Immunocytochemical studies revealed the presence of numerous trkA-immunoreactive astrocytes. **TrkB** mRNA, encoding the full-length high-affinity receptor for BDNF, remained undetectable by non-isotopic in situ hybridization. In contrast to the lack of neurotrophin gene **expression** by glial components of the lesioned VB, dorsal column nuclei neurons contained NGF mRNA as revealed by in situ hybridization studies at 10 days--prior to enhanced LNGFR **expression** in the lesion--and 2 months post-lesion. In addition, the number and the staining...
Descriptors: Axons--metabolism--ME; *Brain--metabolism--ME; *Gene **Expression**; *Nerve Growth Factors--biosynthesis--BI; *Neuroglia --metabolism--ME; *Neurons--metabolism--ME; *Receptors, Nerve Growth Factor

...

6/3,K,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07812846 93343923 PMID: 8343154
trk immunoreactivity at neuronal dendrite and cell body.
Okazawa H; Nishiyama K; Kamei M; Washizaki K; Murayama S; Kwak S; Kanazawa I
Department of Neurology, Faculty of Medicine, University of Tokyo, Japan.
Biochemical and biophysical research communications (UNITED STATES) Jul 30 1993, 194 (2) p683-90, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neurotrophins homologous to the nerve growth factor (NGF) bind the neurotrophic receptors of the trk gene family. Since the target tissues release these neurotrophic factors to the neuron, it has been believed that their trophic effects are mediated by the retrograde axonal transport. However it remains an open question whether the neurotrophins act through the autocrine or the paracrine mechanisms, since the protein-level **expression** of trk has not been studied so far. We have made polyclonal antibodies against the recombinant proteins of chicken trkC and rat **trkB** . These antibodies showed immunoreactivity at the dendrite and the cell body of neuron. This subcellular localization strongly suggests the autocrine or the paracrine mechanism of the neurotrophic factors. At the same time, our data provide basic knowledge to decide where to deliver these neurotrophic factors in the therapy of **neurodegenerative** diseases.

... whether the neurotrophins act through the autocrine or the paracrine mechanisms, since the protein-level **expression** of trk has not been studied so far. We have made polyclonal antibodies against the recombinant proteins of chicken trkC and rat **trkB** . These antibodies showed immunoreactivity at the dendrite and the cell body of neuron. This subcellular...

... provide basic knowledge to decide where to deliver these neurotrophic factors in the therapy of **neurodegenerative** diseases.
Gene Symbol: trk; **trkB**; trkC

6/3,K,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07735063 93261547 PMID: 8492907
Systemic interleukin-1 beta decreases brain-derived neurotrophic factor messenger RNA **expression** in the rat hippocampal formation.
Lapchak P A; Araujo D M; Hefti F
Division of Neurogerontology, Andrus Gerontology Center, University of Southern California, Los Angeles 90089-0191.
Neuroscience (ENGLAND) Mar 1993, 53 (2) p297-301, ISSN 0306-4522 Journal Code: 7605074
Contract/Grant No.: AG09793; AG; NIA; AG10480; AG; NIA; NS22933; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Brain-derived neurotrophic factor is selectively **expressed** at relatively high levels in the rat hippocampal formation (for review, see Ref. 12; see also Refs 8, 13, 19, 20, 27) where it is thought to be

involved in mechanisms of **neurodegeneration** and/or neural protection related to the plasticity of hippocampal neurons. Functional responses to brain-derived neurotrophic factor appear to be mediated by a tyrosine receptor kinase B with the possible involvement of the p75 low-affinity nerve growth factor receptor protein. Among the many characteristics of Alzheimer's disease is an upregulation of immune mediators in and around senile plaques in Alzheimer's disease. Recently, interleukin-1 has been shown to be detrimental to the long-term survival of embryonic hippocampal neurons in culture. Thus, if the same occurs in vivo, it is possible that the accumulation of interleukin-1 in Alzheimer's disease hippocampus may be responsible for altered hippocampal neuron synaptic plasticity. This may occur either by a direct action of interleukin-1 on hippocampal neurons or possibly indirectly by stimulating beta-amyloid production. Other indirect mechanisms may involve growth or survival factors such as the neurotrophin brain-derived neurotrophic factor which is thought to play an important role in the plastic responses of hippocampal neurons. A recent study showed that brain-derived neurotrophic factor mRNA is selectively decreased in the dentate gyrus in Alzheimer's disease. The reason(s) for the decrease of brain-derived neurotrophic factor mRNA is not known, but one possibility may be associated with the enhanced **expression** of interleukin-1 in the hippocampus of Alzheimer's disease patients.(ABSTRACT TRUNCATED AT 250 WORDS)

Systemic interleukin-1 beta decreases brain-derived neurotrophic factor messenger RNA **expression** in the rat hippocampal formation.

Brain-derived neurotrophic factor is selectively **expressed** at relatively high levels in the rat hippocampal formation (for review, see Ref. 12; see...

...8, 13, 19, 20, 27) where it is thought to be involved in mechanisms of **neurodegeneration** and/or neural protection related to the plasticity of hippocampal neurons. Functional responses to brain...

... neurotrophic factor mRNA is not known, but one possibility may be associated with the enhanced **expression** of interleukin-1 in the hippocampus of Alzheimer's disease patients.(ABSTRACT TRUNCATED AT 250...

Gene Symbol: **trkb**

6/3,K,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07729188 93254635 PMID: 8487914

BDNF and **trkB** mRNA **expression** in the hippocampal formation of aging rats.

Lapchak P A; Araujo D M; Beck K D; Finch C E; Johnson S A; Hefti F

Division of Neurogerontology, Andrus Gerontology Center, University of Southern California, Los Angeles 90089-0191.

Neurobiology of aging (UNITED STATES) Mar-Apr 1993, 14 (2) p121-6, ISSN 0197-4580 Journal Code: 8100437

Contract/Grant No.: AG09793; AG; NIA; AG10480; AG; NIA; NS22933; NS; NINDS; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Quantitative in situ hybridization and northern blot analysis techniques were used to determine the topographical distribution and levels of mRNA coding for brain-derived neurotrophic factor (BDNF) and the tyrosine receptor kinase (**trkB**) mRNA in the hippocampal formation of two strains of male rat during aging. Age did not change the prevalence or regional distribution patterns of BDNF or **trkB** mRNA in the hippocampal formation throughout the lifespan of male Sprague-Dawley rats. There also were no significant differences in the prevalence or

topographical distribution patterns of **trkB** mRNA transcripts during aging. Northern blot analysis of hippocampal RNA from male Fischer 344 confirmed that neither BDNF mRNA nor **trkB** mRNA levels changed with age. These findings suggest that age-related **neurodegenerative** changes, including the atrophy of the cholinergic septo-hippocampal pathway, are not the result of changes in hippocampal BDNF or **trkB** mRNA **expression** . Moreover, the prevalence and distribution of synaptosomal-associated protein 25 (SNAP-25), a neuron-specific protein located in synaptic terminals and a putative marker of synaptic integrity, did not change with age. These findings indicate that altered hippocampal synaptic plasticity which occurs in the aged rat brain is not a reflection of changes in the **expression** of BDNF or **trkB** receptor mRNA.

BDNF and **trkB** mRNA **expression** in the hippocampal formation of aging rats.

...levels of mRNA coding for brain-derived neurotrophic factor (BDNF) and the tyrosine receptor kinase (**trkB**) mRNA in the hippocampal formation of two strains of male rat during aging. Age did not change the prevalence or regional distribution patterns of BDNF or **trkB** mRNA in the hippocampal formation throughout the lifespan of male Sprague-Dawley rats. There also were no significant differences in the prevalence or topographical distribution patterns of **trkB** mRNA transcripts during aging. Northern blot analysis of hippocampal RNA from male Fischer 344 confirmed that neither BDNF mRNA nor **trkB** mRNA levels changed with age. These findings suggest that age-related **neurodegenerative** changes, including the atrophy of the cholinergic septo-hippocampal pathway, are not the result of changes in hippocampal BDNF or **trkB** mRNA **expression** . Moreover, the prevalence and distribution of synaptosomal-associated protein 25 (SNAP-25), a neuron-specific...

...which occurs in the aged rat brain is not a reflection of changes in the **expression** of BDNF or **trkB** receptor mRNA.

; Blotting, Northern; Brain-Derived Neurotrophic Factor; Gene **Expression**; In Situ Hybridization; Nerve Growth Factors--genetics--GE ; Nerve Tissue Proteins--genetics--GE; Neuronal Plasticity...

Gene Symbol: BDNF; **trkB**

6/3,K,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07467254 92407909 PMID: 1326636

Function and evolution in the NGF family and its receptors.

Ebendal T
Department of Developmental Biology, Uppsala University, Sweden.

Journal of neuroscience research (UNITED STATES) Aug 1992, 32 (4) p461-70, ISSN 0360-4012 Journal Code: 7600111
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The gene family of neurotrophins includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Recently, neurotrophin-5 (NT-5), a possible mammalian homologue to NT-4 described in the frog Xenopus, has been cloned in man and rat. The neurotrophins stimulate survival and differentiation of a range of target neurons by binding to cell surface receptors. The structure of NGF has recently been clarified from crystallographic data. The similarities between the different neurotrophins are substantial with the variable regions, giving specificity to each of the family members, being localized to some exposed loop regions. Low-affinity binding (Kd of 10(-9) M) of all tested neurotrophins is mediated via a 75 K glycoprotein (LNGFR) that has been cloned and characterized. A 140 K tyrosine protein kinase encoded by the proto-oncogene trk has been found to bind NGF with

high affinity (Kd of 10(-11) M) and to evoke the cellular neurotrophic responses. In addition, a protein encoded by the trk-related gene **trkB** has been shown to bind BDNF. Recently, a third member of the trk family, trkC, has been cloned and demonstrated to function as a high-affinity receptor for NT-3. The **expression** of trk and LNGFR mRNA are co-localized in the rat brain to the medial septal nucleus and the nucleus of Broca's diagonal band containing the NGF-responsive magnocellular cholinergic neurons projecting to hippocampus and cerebral cortex. In sharp contrast, the pattern of **expression** of **trkB** is widely spread in many areas of the cortex as well as lateral septum. The **trkB** protein might serve general functions in large areas of the cortex. Site-directed mutagenesis and **expression** of recombinant chimaeric neurotrophin proteins have made it possible to localize a likely region for the interaction between NGF and the LNGFR. This region could be altered, resulting in the total loss of LNGFR binding by the mutant NGF protein without affecting the binding to the trk receptor which was sufficient for the full biological activity. Cladistic analysis of likely phylogenies within the neurotrophins shows BDNF and NT-4 to be most closely related whereas NGF may be the sister group to NT-3, BDNF, and NT-4. Neurotrophins offer obvious clinical possibilities for treatment of **neurodegenerative** diseases.

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...been cloned and demonstrated to function as a high-affinity receptor for NT-3. The **expression** of trk and LNGFR mRNA are co-localized in the rat brain to the medial...

...magnocellular cholinergic neurons projecting to hippocampus and cerebral cortex. In sharp contrast, the pattern of **expression** of **trkB** is widely spread in many areas of the cortex as well as lateral septum. The **trkB** protein might serve general functions in large areas of the cortex. Site-directed mutagenesis and **expression** of recombinant chimaeric neurotrophin proteins have made it possible to localize a likely region for...

... to NT-3, BDNF, and NT-4. Neurotrophins offer obvious clinical possibilities for treatment of **neurodegenerative** diseases.

(0/8

6/3,K,AB/24 (Item 1 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

13373793 BIOSIS NO.: 200200002614
Distribution of **trkB**.tc and **trkB**.fl in PD and DLBD.
AUTHOR: Fenner B M(a); Hammond R R; Achim C L(a)
AUTHOR ADDRESS: (a)Pathology, Univ of Pittsburgh, Pittsburgh, PA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (2):p2113 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Brain derived neurotrophic factor(BDNF) is abundantly **expressed** in the CNS and is considered to have the potential to be both a therapeutic agent and be also implicated in the progress of chronic brain degeneration (e.g. Parkinson's disease (PD) and dementia with lewy body disease(DLBD)). The effects of BNDF are mediated by its binding to either the truncated(**trkB**.tc) or full-length(**trkB**

.fl) **trkB** receptor. We hypothesize that in response to neuronal degeneration, the upregulation of **trkB** receptors and the distribution pattern of full-length vs truncated isoforms will have unique features depending on region and possibly underlying disease. Paraffin embedded sections of cortex, hippocampus, striatum, and substantia nigra tissue from PD, DLBD, and age matched control cases were analyzed by immunohistochemistry and immunofluorescent laser confocal microscopy(IFLCM). Tissue sections were single- and double-labeled with antibodies against **trkB**.tc, **trkB**.fl, HLADR, and alpha-synuclein. Current studies analyze the localization of **trkB** in relation to tyrosine hydroxylase, dopamine transporter, and dopamine receptors. Preliminary data show extensive perivascular **trkB**.fl **expression** localized predominantly to microglia and to a lesser extent, astrocytes. In regions of extensive **trkB**.fl labeling, sparse neuronal labeling was observed. **TrkB**.tc localization to glial cells was also perivascular, but its distribution was punctate. There was extensive punctate localization of **trkB**.tc in the degenerating neurons of the substantia nigra and striatum. The differential localization of **trkB**.tc from **trkB**.fl supports the hypothesis that these receptors may perform distinct functions in **neurodegeneration**.

2001

Distribution of **trkB**.tc and **trkB**.fl in PD and DLBD.

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DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...**expression**; ...

...**trkB**.fl...

...distribution, **expression**, localization, regulation...

...**trkB**.tc...

...distribution, **expression**, localization, regulation

6/3,K,AB/25 (Item 2 from file: 55)

DIALOG(R)File 55:Biosis Previews(R)

13275121 BIOSIS NO.: 200100482270
Natural product-derived small molecule activators of the Trk neurotrophin receptors.
AUTHOR: Pollack S J(a); Lee V(a); Wingrove P(a); Hefti F(a); Ellis S(a); Wilkie N(a)
AUTHOR ADDRESS: (a)Dept of Molecular Biology, Merck Sharp and Dohme, Harlow **UK
JOURNAL: Society for Neuroscience Abstracts 27 (1):p356 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The Trk family of receptors each have preferred neurotrophin ligands: NGF binds preferentially to TrkA, BDNF and NT-4 bind to **TrkB** and NT-3 binds to TrkC. Following neurotrophin binding to the extracellular surface of these receptors, they homodimerize and transphosphorylate their intracellular kinase domains. This, in turn, triggers the activation of multiple signalling cascades, culminating in the neuroregenerative effects associated with the neurotrophins: increased neuronal survival and neurite outgrowth. Since neurotrophins themselves are poor drug targets due to their poor pharmacokinetic behaviour and bioavailability, small molecule neurotrophin mimetics could be beneficial in treating a number of **neurodegenerative** disorders, including Parkinson's Disease and Alzheimer's Disease. We will present data describing how a range of compounds from natural sources stimulated Trk receptor phosphorylation in both primary neuronal cultures and CHO cells **expressing** human Trk receptors. Compounds stimulated Trk receptor phosphorylation to about 70% of the maximal phosphorylation produced by the relevant neurotrophin for each receptor subtype. Further experiments utilising transiently transfected PDGF/TrkA and TrkA/PDGF receptor chimeras, demonstrated that the compounds were binding to the intracellular domain of the TrkA receptor. Thus, small molecule natural products have been identified that activate Trk receptor phosphorylation by interacting at sites different from the neurotrophin-binding site. The neurotrophic properties of these compounds are currently under investigation.

2001
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DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...chimeras, **expression**, intracellular domain, neurotrophin receptor, phosphorylation, regulation, subtypes...

6/3,K,AB/26 (Item 3 from file: 55)

12927366 BIOSIS NO.: 200100134515
The effect of oxidative stress on TrkA and **TrkB expression** in SHSY5Y neuroblastoma cells.
AUTHOR: Olivieri G(a); Savaskan E; Otten U; Kunz D; Bruttel S; Brack C; Mueller-Spahn F
AUTHOR ADDRESS: (a)Psychiatric University Clinic, Basel, CH**Switzerland
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-7951 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Oxidative stress and the generation of reactive oxygen species are increasingly being implicated as causative agents in **neurodegenerative** diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and Alzheimer's disease (AD). Abeta 1-42, a hallmark molecule in AD, has been shown to induce oxidative stress and to affect intracellular H2O2 production. The treatment of neuronal cells with neurotrophins such as nerve growth factor (NGF), which primarily interacts with Trk A, protects cells from Abeta-induced toxicity. Furthermore, NGF treatment protects against H2O2-induced toxicity by increasing intracellular glutathione (GSH) levels. In the present study we examined the effects of Abeta 1-42 (1 muM) and H2O2 (50 muM) on the **expression** of Trk A and Trk B receptors in SHSY5Y neuroblastoma cells. The results show that both Abeta and H2O2 are able to induce oxidative stress (as measured by a loss of cellular GSH) and cell cytotoxicity (MTT assay). Western analysis of stressed cells showed a time-dependent loss of Trk A and Trk B from the cell surface. Trk B **expression** showed an initial increase followed by a sharp decline to levels below controls after exposure to Abeta 1-42. Changes were also observed in the **expression** of Trk A and Trk B mRNA after exposure to Abeta 1-42 and H2O2. The role of antioxidants, such as N-Acetyl-cysteine (NAC) and melatonin, on the **expression** Trk receptors was also investigated. These data indicate that molecules such as Abeta and H2O2, which induce oxidative stress, could modulate the **expression** of Trk receptors thereby influencing the specific actions of neurotrophins.
2000

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DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...**expression**; ...

...**expression**; ...

...TrkB--...

...**expression**; **TrkB**...

...TrkB receptor...

...**expression**;

6/3,K,AB/27 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

12881029 BIOSIS NO.: 200100088178
Dual effects of brain-derived neurotrophic factor on survival of dopaminergic neurons in vitro.
AUTHOR: Park J S; Lee J J; Yeon D S
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-31912 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Under the conditions of Parkinson's disease (PD), activated microglia produces cytokines that may cause dopaminergic **neurodegeneration** in the substantia nigra (SN). It has been reported that activated microglias **expressed** increased amount of brain derived neurotrophic factor (BDNF), and that a high level of **TrkB**, BDNF receptor, was **expressed** normally in dopaminergic neurons of SN. From these observations, it is possible to speculate that the excess amount of BDNF may lead to the death of SN dopaminergic neurons. We investigated effects of different concentrations of BDNF on the survival of dopaminergic neurons in SN. Cells were isolated from SN of fetal rats (E-14) and cultured in 10% FBS-containing DMEM medium (control). Cells were then cultured for 10 days in the presence of different doses of BDNF (10, 50, 100, 200, 300 ng/ml). Dopamin-ergic neurons were identified using immunohistochemistry for tyrosine hydroxyl-ase (TH), and survived neurons were measured by counting TH-reactive cells. As compared to the control cultured in BDNF-free medium, the number of TH-cells increased gradually until 3 days in the presence of low doses of BDNF (10, 50, 100 ng/ml) and decreased thereafter. In the presence of high doses of BDNF (200, 300 ng/ml), however, TH-cells decreased in number continuously up to 10 days of the test period. The results suggest that the excess amount of BDNF that is perhaps released from activated microglia in the PD states may participate in the degenerative processes of dopaminergic neurons in SN.

2000

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DESCRIPTORS:
...ORGANISMS: PARTS ETC: nervous system, **neurodegeneration**, survival...
CHEMICALS & BIOCHEMICALS: **TrkB**;

6/3,K,AB/28 (Item 5 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

10672396 BIOSIS NO.: 199799293541
Trk receptor alterations in Alzheimer's disease.
AUTHOR: Connor B; Young D; Lawlor P; Gai W; Waldvogel H; Faull R L M; Dragunow M(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Sch. Med., Univ. Auckland, Private Bag 92019, Auckland**New Zealand
JOURNAL: Molecular Brain Research 42 (1):p1-17 1996
ISSN: 0169-328X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The **expression** of trk receptors in postmortem normal, Huntington's disease and Alzheimer's disease human brains was investigated using immunohistochemistry, in-situ hybridisation and Western blotting. Alzheimer's disease hippocampi displayed an increase in trkA receptor levels in astrocytes in the CA1 region, some of which were associated with beta-amyloid-positive plaques. Truncated **trkB** receptors were found in high levels in senile plaques, while the full-length receptor was **expressed** in glial-like cells in the hippocampus of Alzheimer's disease brains. In-situ hybridisation studies indicated that trk receptor mRNA was also elevated in Alzheimer's. The appearance of trkA and **trkB** receptors in astrocytes and plaques in Alzheimer's disease might be related to beta-amyloid deposition and could be implicated in the development of Alzheimer's disease.

1996

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MISCELLANEOUS TERMS: ...**NEURODEGENERATION**;

6/3,K,AB/29 (Item 6 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

09057630 BIOSIS NO.: 199497066000
Molecular cloning and **expression** of human trk, **trkB**, and trkC.
AUTHOR: Shelton D L(a); Sutherland J; Carroll K; Broz S
AUTHOR ADDRESS: (a)Dep. Neurosci., Genentech Inc., South San Francsico, CA 94080**USA
JOURNAL: Society for Neuroscience Abstracts 19 (1-3):p1301 1993
CONFERENCE/MEETING: 23rd Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 7-12, 1993
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
1993

Molecular cloning and **expression** of human trk, **trkB**, and trkC.
MISCELLANEOUS TERMS: ...**NEURODEGENERATIVE** DISEASE

6/3,K,AB/30 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10516471 Genuine Article#: 535BU Number of References: 53
Title: Failure of brain-derived neurotrophic factor-dependent neuron survival in mouse trisomy 16 (ABSTRACT AVAILABLE)
Author(s): Dorsey SG; Bambrick LL; Balice-Gordon RJ; Krueger BK (REPRINT)
Corporate Source: Univ Maryland,Sch Med, Dept Physiol,655 W Baltimore St/Baltimore//MD/21201 (REPRINT); Univ Maryland,Sch Med, Dept Physiol,Baltimore//MD/21201; Univ Maryland,Sch Med, Dept Anesthesiol,Baltimore//MD/21201; Univ Maryland,Sch Nursing,Baltimore//MD/21201; Univ Maryland,Program Neurosci,Baltimore//MD/21201; Univ Penn,Sch Med, Dept Neurosci,Philadelphia//PA/19104
Journal: JOURNAL OF NEUROSCIENCE, 2002, V22, N7 (APR 1), P2571-2578
ISSN: 0270-6474 Publication date: 20020401
Publisher: SOC NEUROSCIENCE, 11 DUPONT CIRCLE, NW, STE 500, WASHINGTON, DC 20036 USA
Language: English Document Type: ARTICLE
Abstract: The neurotrophin, brain derived neurotrophic factor (BDNF), exerts multiple effects on the development and maintenance of the nervous system, including regulating synaptic plasticity and promoting neuron survival. Here we report the selective failure of BDNF-dependent survival in cultured hippocampal neurons from the trisomy 16 (Ts16) mouse, an animal model of Down syndrome. This failure is accompanied by overexpression of a truncated, kinase-deficient isoform (T1) of the BDNF receptor tyrosine receptor kinase B (**trkB**). Adenovirus-mediated introduction of exogenous full-length **trkB** into Ts16 neurons fully restored BDNF-dependent survival, whereas exogenous truncated **trkB expression** in normal, euploid neurons reproduced the Ts16 BDNF signaling failure. Thus, the failure of Ts16 neurons to respond to BDNF is caused by dysregulation of **trkB** isoform **expression**. Such a neurotrophin signaling defect could contribute to developmental and degenerative disorders of the nervous system.

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...Identifiers--TRUNCATED **TRKB** RECEPTORS; HIPPOCAMPAL-NEURONS;

SIGNAL-TRANSDUCTION; SYNAPTIC PLASTICITY; NERVOUS-SYSTEM; DOWNS-SYNDROME; FULL-LENGTH; ALZHEIMERS-DISEASE...

6/3,K,AB/31 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08361454 Genuine Article#: 276RY Number of References: 125
Title: The therapeutic potential of neurotrophins for the treatment of diabetic neuropathy (ABSTRACT AVAILABLE)
Author(s): Fernyhough P (REPRINT) ; Tomlinson DR
Corporate Source: UNIV MANCHESTER,SCH BIOL SCI, DIV NEUROSCI, 1-124 STOPFORD BLDG, OXFORD RD/MANCHESTER M13 9PT/LANCS/ENGLAND/ (REPRINT)
Journal: DIABETES REVIEWS, 1999, V7, N4, P300-311
ISSN: 1066-9442 Publication date: 19990000
Publisher: AMER DIABETES ASSOC, 1660 DUKE ST, ALEXANDRIA, VA 22314
Language: English Document Type: REVIEW
Abstract: Sensory neuron dysfunction is a hallmark of symmetrical diabetic polyneuropathy: Taken together, the clinical and pathological features of this condition give a picture of a distal degeneration, with progressive loss of sensation from both myelinated and unmyelinated primary afferents. Direct consequences of hyperglycemia, such as protein glycation and exaggerated flux through the sorbitol pathway, form one level of possible etiological components. tit the nest level-links between disordered biochemistry and **neurodegeneration** -a promising candidate is impaired neurotrophic support from nerve growth factor (NGF), neurotrophin-3 (NT-3), and brain-derived neurotrophic factor (BDNF). Studies focused on unmyelinated sensory fiber dysfunction in streptozocin (STZ) induced diabetic rats have established a role for deficient NGF **expression** in target tissues of the lower limb. The NGF-dependent (trkA-**expressing**) C-fiber subpopulation of unmyelinated neurons show reduced retrograde axonal transport of NGF to the lumbar dorsal root ganglia (DRG) and reduced **expression** of the neuropeptides substance P and calcitonin gene-related peptide (CGRP), The majority of larger myelinated sensory fibers, Which appear to be particularly sensitive to diabetes-related dysfunction? are unresponsive to NGF and do not **express** the trkA receptor, indeed, the available evidence indicates that these fibers **express trkB** and/or trkC and that maintenance of their phenotype may depend on BDNF and/or NT-3, Recent studies show that target tissue **expression** of NT-3 and BDNF is altered and retrograde axonal transport within the sciatic nerve is depressed in STZ diabetic rats. This review will discuss the current status of NGF work, with special reference to recent clinical trials. Also, new developments in understanding the effects of loss of NT-3 and/or BDNF dependent neurotrophic support on large myelinated sensory fiber function will be presented.

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...Identifiers--NERVE GROWTH-FACTOR; RETROGRADE AXONAL-TRANSPORT; ADULT SENSORY NEURONS; DORSAL-ROOT GANGLIA; NEUROFILAMENT GENE-**EXPRESSION**; FACTOR MESSENGER-RNA; RAT SCIATIC-NERVE; SUBSTANCE-P; SIGNAL-TRANSDUCTION; TRK RECEPTORS

6/3,K,AB/32 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07421812 Genuine Article#: 163PE Number of References: 205
Title: Distribution and retrograde transport of trophic factors in the central nervous system: Functional implications for the treatment of **neurodegenerative** diseases (ABSTRACT AVAILABLE)
Author(s): Mufson EJ (REPRINT) ; Kroin JS; Sendera TJ; Sobreviela T
Corporate Source: RUSH PRESBYTERIAN ST LUKES MED CTR,RUSH ALZHEIMERS DIS CTR, RES CTR BRAIN REPAIR/CHICAGO//IL/60612 (REPRINT); RUSH PRESBYTERIAN ST LUKES MED CTR,RUSH ALZHEIMERS DIS CTR, RES CTR BRAIN REPAIR, DEPT NEUROSURG/CHICAGO//IL/60612
Journal: PROGRESS IN NEUROBIOLOGY, 1999, V57, N4 (FEB), P451-484
ISSN: 0301-0082 Publication date: 19990200
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND
Language: English Document Type: REVIEW
Abstract: Neurotrophins play a crucial role in the maintenance, survival and selective vulnerability of various neuronal populations within the normal and diseased brain. Several families of growth promoting substances have been identified within the central nervous system (CNS) including the superfamily of nerve growth factor related neurotrophin factors, glial derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF). In addition, other non-neuronal growth factors such as fibroblast growth factor (FGF) have also been identified.

This article reviews the trophic anatomy of these factors within the CNS. Intraventricular and intra-parenchymal injections of exogenous nerve growth factor result in retrograde labeling mainly within the cholinergic basal forebrain.

Distribution of brain derived neurotrophic factor (BDNF) following intraventricular injection is minimal due to the binding to the **trkB** receptor along the ventricular wall. In contrast, intraparenchymal injections of BDNF results in widespread retrograde transport throughout the CNS. BDNF has also been shown to be transported anterogradely within the CNS. Infusion of GDNF into the CNS results in retrograde transport limited to the nigrostriatal pathway.

Hippocampal injections of NT-3 retrogradely label mainly basal forebrain neurons. Retrograde trans port of radiolabeled CNTF has only been observed in sensory neurons of the sciatic nerve. Following intraventricular and intraparenchymal infusion of radiolabeled bFGF, retrograde neuronal labeling was found in the telecephalon, diencephalon, mesencephalon and pens. In contrast retrograde labeling for aFGF was found only in the hypothalamus and midbrain.

Since select neurotrophins traffic anterogradely and retrogradely within the nervous system, these proteins could be used to treat neurological diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. (C) 1999 Elsevier Science Ltd. All

...Title: transport of trophic factors in the central nervous system: Functional implications for the treatment of **neurodegenerative** diseases
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...Identifiers--SCLEROSIS; PROGRESSIVE MOTOR NEURONOPATHY; MIDBRAIN DOPAMINERGIC-NEURONS; SEPTAL CHOLINERGIC NEURONS; FIMBRIA-FORNIX TRANSECTION; MESSENGER-RNA **EXPRESSION**; BASAL FOREBRAIN NEURONS; CELL-SURFACE RECEPTORS

6/3,K,AB/33 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06830098 Genuine Article#: ZV232 Number of References: 59
Title: Inhibition of phosphorylation of **trkB** and trkC and their signal transduction by alpha(2)-macroglobulin (ABSTRACT AVAILABLE)
Author(s): Hu YQ; Koo PH (REPRINT)
Corporate Source: NE OHIO UNIV,COLL MED, DEPT MICROBIOL & IMMUNOL, POB 95/ROOTSTOWN//OH/44272 (REPRINT); NE OHIO UNIV,COLL MED, DEPT MICROBIOL & IMMUNOL/ROOTSTOWN//OH/44272
Journal: JOURNAL OF NEUROCHEMISTRY, 1998, V71, N1 (JUL), P213-220
ISSN: 0022-3042 Publication date: 19980700
Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106
Language: English Document Type: ARTICLE
Abstract: Monoamine-activated alpha(2)-macroglobulin (alpha(2)M) was shown to reduce the dopamine concentration in corpus striatum of adult rat brains and inhibit other neuronal functions in vivo and in vitro. As brain-derived neurotrophic factor, neurotrophin-4, and neurotrophin-3 are important neurotrophic factors for dopaminergic neurons, the effect of monoamine-activated alpha(2)M on signal transduction by **trkB** and trkC was investigated. The results show that monoamine-activated alpha(2)M binds to **trkB** and inhibits brain-derived neurotrophic factor/neurotrophin-4-promoted autophosphorylation of **trkB** in a dose-dependent manner in both **trkB-expressing** NIH3T3 (NIH3T3-**trkB**) and human neuroblastoma SH-SY5Y cells. Monoamine-activated alpha(2)M also blocks tyrosine phosphorylation of phospholipase C-gamma 1 and extracellular signal-regulated protein kinase(ERK)-1,which are key intracellular proteins involved in **trkB** signal transduction. Similarly, monoamine-activated alpha(2)M inhibits tyrosine phosphorylation of neurotrophin-3-induced trkC and its signal transduction in a dose-dependent manner in NIH3T3 cells **expressing** trkC (NIH3T3-trkC). In contrast to monoamine-activated alpha(2)M, normal alpha(2)M has little or no significant inhibitory effect on the phosphorylation of **trkB** and trkC. In addition, the retinoic acid-promoted tyrosine phosphorylation of phospholipase C-gamma 1, ERK-1, and/or ERK-2 in SH-SY5Y cells was unaffected by monoamine-activated alpha(2)M; this suggests that the inhibitory effect of activated alpha(2)M on the neurotrophin-stimulated phosphorylation of intracellular signalling proteins may be specific. Taken together, the data indicate that activated alpha(2)M is a pan-trk inhibitor, which by virtue of its binding to trk receptors may block trk-mediated signal transduction in dopaminergic neurons and lead to reduction of dopamine concentration in corpus striatum.

Title: Inhibition of phosphorylation of **trkB** and trkC and their signal transduction by alpha(2)-macroglobulin
...Abstract: for dopaminergic neurons, the effect of monoamine-activated

alpha(2)M on signal transduction by **trkB** and trkC was investigated. The results show that monoamine-activated alpha(2)M binds to **trkB** and inhibits brain-derived neurotrophic factor/neurotrophin-4-promoted autophosphorylation of **trkB** in a dose-dependent manner in both **trkB-expressing** NIH3T3 (NIH3T3-**trkB**) and human neuroblastoma SH-SY5Y cells. Monoamine-activated alpha(2)M also blocks tyrosine phosphorylation...

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6/3,K,AB/34 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06442575 Genuine Article#: YT570 Number of References: 52
Title: Free radical scavenging and inhibition of nitric oxide synthase potentiates the neurotrophic effects of brain-derived neurotrophic factor on axotomized retinal ganglion cells in vivo (ABSTRACT AVAILABLE)
Author(s): Klocker N; Cellerino A; Bahr M (REPRINT)
Corporate Source: UNIV TUBINGEN,DEPT NEUROL, HOPPE SEYLER STR 3/D-72076 TUBINGEN//GERMANY/ (REPRINT); UNIV TUBINGEN,DEPT NEUROL/D-72076 TUBINGEN//GERMANY/; UNIV TUBINGEN,DEPT OPHTHALMOL/D-72076 TUBINGEN//GERMANY/
Journal: JOURNAL OF NEUROSCIENCE, 1998, V18, N3 (FEB 1), P1038-1046
ISSN: 0270-6474 Publication date: 19980201
Publisher: SOC NEUROSCIENCE, 11 DUPONT CIRCLE, NW, STE 500, WASHINGTON, DC 20036
Language: English Document Type: ARTICLE
Abstract: Brain-derived neurotrophic factor (BDNF) partially promotes the survival of axotomized retinal ganglion cells (RGCs). In analogy with in vitro experiments (Koh et al., 1995; Samdami et al., 1996), we tested whether neuroprotection by BDNF is limited by adverse effects as a consequence of excessive free radical formation. First, we investigated whether BDNF and the free radical scavenger N-tert-butyl-(2-sulfophenyl)-nitrone (S-PBN) cooperate in protecting RGCs from axotomy-induced death. Although systemic S-PBN treatment alone did not influence RGC survival after axotomy, it potentiated the neuroprotective effects of BDNF significantly. Single BDNF treatment rescued 27% of the RGCs, which otherwise would have died 14 d after optic nerve transection, whereas a combined treatment of BDNF and S-PBN improved this rescue rate up to 68%. We then investigated whether the adverse effects of BDNF could be ascribed to activation of nitric oxide synthase (NOS). We found colocalization of NOS and the BDNF receptor **TrkB** in the retina. NADPH-diaphorase reactivity, a reliable marker for NOS in the rat retina, increased after chronic BDNF treatment in vivo. Systemic application of the NOS-inhibitor N-omega-nitro-L-arginine-methylester (L-NAME) potentiated the neuroprotective action of BDNF (55% rescue rate). We conclude that activation of NOS is a pathological consequence of BDNF application, which reduces its neuroprotective potential. The observation that this adverse effect can be antagonized by systemic application of free radical scavengers could be of relevance for clinical applications of neurotrophins in human **neurodegenerative** diseases.

...Abstract: activation of nitric oxide synthase (NOS). We found colocalization of NOS and the BDNF receptor **TrkB** in the retina. NADPH-diaphorase reactivity, a reliable marker for NOS in the rat retina...

...of free radical scavengers could be of relevance for clinical applications of neurotrophins in human **neurodegenerative** diseases.
...Identifiers--ADULT-RAT RETINA; OPTIC-NERVE; NADPH-DIAPHORASE; SUPERIOR COLLICULUS; NEONATAL RATS; IN-VIVO; SURVIVAL; NEURONS; **EXPRESSION**; DEATH

6/3,K,AB/35 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05786112 Genuine Article#: WX540 Number of References: 47
Title: Ligand-induced down-regulation of Trk messenger RNA, protein and tyrosine phosphorylation in rat cortical neurons (ABSTRACT AVAILABLE)
Author(s): Knusel B (REPRINT) ; Gao H; Okazaki T; Yoshida T; Mori N; Hefti F; Kaplan DR
Corporate Source: UNIV SO CALIF,DIV NEUROGERONTOL, ANDRUS GERONTOL CTR/LOS ANGELES//CA/90089 (REPRINT); UNIV SO CALIF,DEPT SCI BIOL/LOS ANGELES//CA/90089; NCI,FREDERICK CANC RES & DEV CTR, ABL BASIC RES PROGRAM, EUKARYOT SIGNAL TRANSD/FREDERICK//MD/21702
Journal: NEUROSCIENCE, 1997, V78, N3 (JUN), P851-862
ISSN: 0306-4522 Publication date: 19970600
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB
Language: English Document Type: ARTICLE
Abstract: Chronic exposure of brain neurons to nerve growth factor in vitro and in vivo results in increased levels of the nerve growth factor receptor TrkA. In contrast, in the present study, we have found that chronic exposure of rat embryonic cortical neurons to brain-derived neurotrophic factor (BDNF) leads to a pronounced reduction of the levels of protein and messenger RNA for the full-length but not the truncated BDNF receptor **TrkB**. Similar effects were observed with the other **TrkB** ligands neurotrophin-3 and neurotrophin-4/5. After pretreatment with BDNF, neurotrophin-3 or neurotrophin-4/5, subsequent tyrosine phosphorylation responses of the remaining Trks to the same factors were greatly reduced. Three days exposure of rat embryonic cortical neurons to BDNF induced an absolute refractory period of several hours, with no subsequent response to the same factor. Similar but less pronounced refractory effects were observed with neurotrophin-3 and neurotrophin-4/5. Our results suggest a negative regulatory effect of BDNF and other **TrkB** ligands on **TrkB** receptors. Down-regulation of the **TrkB** response by its ligands might play a role in the control of BDNF action during early development, when BDNF levels significantly increase.

Our findings are also of potential clinical relevance, since the possibility of ligand-induced downregulation of the receptor response needs to be addressed when considering BDNF or other neurotrophins for the therapy of **neurodegeneration**. (C) 1997 IBRO.

...Abstract: of protein and messenger RNA for the full-length but not the truncated BDNF receptor **TrkB**. Similar effects were observed with the other **TrkB** ligands neurotrophin-3 and neurotrophin-4/5. After pretreatment with BDNF, neurotrophin-3 or neurotrophin...
...and neurotrophin-4/5. Our results suggest a negative regulatory effect of BDNF and other **TrkB** ligands on **TrkB** receptors.
Down-regulation of the **TrkB** response by its ligands might play a

role in the control of BDNF action during...

...response needs to be addressed when considering BDNF or other neurotrophins for the therapy of **neurodegeneration**. (C) 1997 IBRO.
...Identifiers--AFFINITY NEUROTROPHIN RECEPTOR; FOREBRAIN CHOLINERGIC NEURONS; PC12 CELLS; TRUNCATED RECEPTORS; SIGNAL-TRANSDUCTION; SYMPATHETIC NEURONS; GENE-**EXPRESSION**; NGF RECEPTORS; BRAIN
Research Fronts: 95-2493 002 (LOW-AFFINITY NEUROTROPHIN RECEPTORS; CULTURED BASAL FOREBRAIN CHOLINERGIC NEURONS; TRKA **EXPRESSION**; NGF TRANSGENIC MICE; NERVE GROWTH-FACTOR)

6/3,K,AB/36 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04731112 Genuine Article#: UD778 Number of References: 46
Title: DECREASED **EXPRESSION** OF **TRKB** AND TRKC MESSENGER-RNAS IN SPINAL MOTONEURONS OF AGED RATS (Abstract Available)
Author(s): JOHNSON H; HOKFELT T; ULFHAKE B
Corporate Source: KAROLINSKA INST,DEPT NEUROSCI,DIV NEUROANAT & NEURONAL PLAST/S-17177 STOCKHOLM//SWEDEN/
Journal: EUROPEAN JOURNAL OF NEUROSCIENCE, 1996, V8, N3 (MAR), P494-499
ISSN: 0953-816X
Language: ENGLISH Document Type: ARTICLE
Abstract: Several studies have indicated that a decrease in availability and/or responsiveness to neurotrophin(s) may be of importance in ageing and disease-related **neurodegeneration**. Using in situ hybridization we have studied the mRNA **expression** of the full-length neurotrophin receptors **TrkB** and TrkC in spinal cord motoneurons of aged rats (30 months old) with symptoms of hindlimb incapacity and in young adult rats (2-3 months old). The labelling intensity for **TrkB** of the individual cell profile was decreased by 25% ($P < 0.001$) in both the cervical and lumbar motor nuclei of aged rats. In thoracic motoneurons of aged and young adult rats the difference in **expression** of **TrkB** mRNA was smaller (down by 15%; $P < 0.05$). The labelling for TrkC mRNA was much weaker than that for **TrkB** in both aged and young adult rats, but TrkC mRNA **expression** also seemed to decrease. Comparison of the different motor nuclei along the spinal cord axis revealed that the motoneurons of the L6/S1 nuclei showed the strongest hybridization signal for the two Trk receptors in both aged and young adult rats. The possibility that a decrease in **TrkB** mRNA may contribute to age-related motor disturbances is discussed.

Title: DECREASED **EXPRESSION** OF **TRKB** AND TRKC MESSENGER-RNAS IN SPINAL MOTONEURONS OF AGED RATS
...Abstract: and/or responsiveness to neurotrophin(s) may be of importance in ageing and disease-related **neurodegeneration**. Using in situ hybridization we have studied the mRNA **expression** of the full-length neurotrophin receptors **TrkB** and TrkC in spinal cord motoneurons of aged rats (30 months old) with symptoms of hindlimb incapacity and in young adult rats (2-3 months old). The labelling intensity for **TrkB** of the individual cell profile was decreased by 25% ($P < 0.001$) in both the...

...of aged rats. In thoracic motoneurons of aged and young adult rats the difference in **expression** of **TrkB** mRNA was smaller (down by 15%; $P < 0.05$). The labelling for TrkC mRNA was much weaker than that for **TrkB** in both aged and young adult rats, but TrkC mRNA **expression** also seemed to decrease. Comparison of the different motor nuclei along the spinal cord axis...

...Trk receptors in both aged and young adult rats. The possibility that a decrease in **TrkB** mRNA may contribute to age-related motor disturbances is discussed.
Research Fronts: 94-1764 007 (NEUROTROPHIN RECEPTOR MESSENGER-RNA **EXPRESSION**; NERVE GROWTH-FACTOR; TRK FAMILY)
94-1113 004 (CILIARY NEUROTROPHIC FACTOR; PHENOTYPE OF CULTURED SYMPATHETIC...

6/3,K,AB/37 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03954028 Genuine Article#: QV451 Number of References: 69
Title: SPECIFIC LESIONS IN THE EXTRAPYRAMIDAL SYSTEM OF THE RAT-BRAIN INDUCED BY 3-NITROPROPIONIC ACID (3-NPA) (Abstract Available)
Author(s): PEI G; EBENDAL T
Corporate Source: UNIV UPPSALA,CTR BIOMED,DEPT DEV NEUROSCI,BOX 587/S-75123 UPPSALA//SWEDEN/; UNIV UPPSALA,CTR BIOMED,DEPT DEV NEUROSCI/S-75123 UPPSALA//SWEDEN/
Journal: EXPERIMENTAL NEUROLOGY, 1995, V132, N1 (MAR), P105-115
ISSN: 0014-4886
Language: ENGLISH Document Type: ARTICLE
Abstract: The irreversible mitochondrial toxin 3-nitropropionic acid (3-NPA) is a specific inhibitor of succinate dehydrogenase. We performed stereotaxic unilateral injections of 3-NPA into the nigrostriatal dopaminergic pathway in rats in order to examine its specific effects on the dopamine system. The 3-NPA-treated rats displayed unidirectional apomorphine-induced rotations, suggesting that 3-NPA selectively damages dopaminergic neurons when injected into the nigrostriatal pathway, In situ hybridization 7 weeks postinjection indicated a decrease in tyrosine hydroxylase (TH) mRNA to 30% of the noninjected side in the substantia nigra pars compacta ($P < 0.05$) and decreased to 62% of the noninjected side in the ventral tegmental area (VTA) (nonsignificant) of 3-NPA-lesioned rats. The number of TH mRNA positive cells showed statistically significant decreases in substantia nigra and VTA ($P < 0.001$) within the lesioned side, In contrast, **expression** of mRNAs encoding choline acetyltransferase, p75 low-affinity NGF receptor, neurotrophin tyrosine kinase receptors Trk and **TrkB**, and brain-derived neurotrophic factor showed neuronal sparing in several other regions of the brain, The results suggest that the nigrostriatal dopaminergic system might be selectively vulnerable to 3-NPA and demonstrate that it is possible to employ 3-NPA in a model of partial lesion of the nigrostriatal dopaminergic system resembling early stages of Parkinson's disease. (C) Academic Press, Inc.

...Abstract: decreases in substantia nigra and VTA ($P < 0.001$) within the lesioned side, In contrast, **expression** of mRNAs encoding choline acetyltransferase, p75 low-affinity NGF receptor, neurotrophin tyrosine kinase receptors Trk and **TrkB**, and brain-derived neurotrophic factor showed neuronal sparing in several other regions of the brain...
Research Fronts: 93-0303 003 (RECEPTORS FOR NERVE GROWTH-FACTOR; NEUROTROPHIN-3 MESSENGER-RNA **EXPRESSION**; SENSORY NEURONS; NGF SURVIVAL RESPONSE; RAT PERIPHERAL TRIGEMINAL SYSTEM)
93-8274 002 (6-HYDROXYDOPAMINE-LESIONED...

...93-2063 001 (RAT STRIATUM PRODUCES EXCITOTOXIC LESIONS; MITOCHONDRIAL TOXIN 3-NITROPROPIONIC ACID; NEURONAL INJURY; **NEURODEGENERATIVE** DISORDERS; TOXICITY OF GLUTAMATE)

6/3,K,AB/38 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03560838 Genuine Article#: PM769 Number of References: 57
Title: INTRASTRIATAL INFUSIONS OF BRAIN-DERIVED NEUROTROPHIC FACTOR - RETROGRADE TRANSPORT AND COLOCALIZATION WITH DOPAMINE-CONTAINING SUBSTANTIA-NIGRA NEURONS IN RAT (Abstract Available)
Author(s): MUFSON EJ; KROIN JS; SOBREVIELA T; BURKE MA; KORDOWER JH; PENN RD; MILLER JA
Corporate Source: RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT NEUROL SCI/CHICAGO//IL/60612; RUSH PRESBYTERIAN ST LUKES MED CTR,DEPT NEUROSURG/CHICAGO//IL/60612; RUSH PRESBYTERIAN ST LUKES MED CTR,RUSH ALZHEIMERS DIS CTR/CHICAGO//IL/60612; UNIV ILLINOIS,DEPT ANAT & CELL BIOL/CHICAGO//IL/00000; AMGEN INC/THOUSAND OAKS//CA/91320
Journal: EXPERIMENTAL NEUROLOGY, 1994, V129, N1 (SEP), P15-26
ISSN: 0014-4886
Language: ENGLISH Document Type: ARTICLE
Abstract: The pattern of retrogradely transported BDNF, a member of the nerve growth family of neurotrophins, following intrastriatal infusion was immunohistochemically visualized within the rodent central nervous system. Human recombinant BDNF was infused at a rate of 3 mu g/h for 7 days with an Alzet 2002 minipump prior to sacrifice. Tissue immunohistochemically processed using a turkey anti-BDNF antibody revealed retrogradely transported BDNF within neurons located mainly within the ipsilateral frontoparietal cortex (predominantly layer V), parafascicular and posterior thalamic nuclei, and substantia nigra, pars compacta. Sections dual immunoreacted for BDNF and tyrosine hydroxylase revealed a subpopulation of dopaminergic neurons (approximately 28%) within the pars compacta which contained retrogradely transported BDNF. Experiments in which a mixture of BDNF and the retrograde tracer fluorogold were simultaneously infused for 7 days into the striatum revealed BDNF and fluorogold single-labeled neurons as well as BDNF and fluorogold dual-labeled cells within the substantia nigra, pars compacta. These observations indicate that only a subpopulation of neurons within the substantia nigra retrogradely transport BDNF following intrastriatal infusion and thus only a subpopulation of cells may be responsive to the trophic influences of BDNF. The retrograde transport of trophins, such as BDNF, represents a unique neuroanatomical tool to selectivity map the location of specific neurotrophin-responsive systems. Unraveling the trophic anatomy of BDNF will aid in understanding its role in development, degeneration, and experimental animal models of regeneration providing essential data for its use in clinical **neurodegenerative** disorders including Parkinson's disease. (C) 1994 Academic Press, Inc.

...Abstract: degeneration, and experimental animal models of regeneration providing essential data for its use in clinical **neurodegenerative** disorders including Parkinson's disease. (C) 1994 Academic Press, Inc.
...Identifiers--NERVE GROWTH-FACTOR; FACTOR RECEPTOR IMMUNOREACTIVITY; MESSENGER-RNA **EXPRESSION**; BASAL FOREBRAIN; CHOLINERGIC NEURONS; TYROSINE KINASE; SPINAL-CORD; ALZHEIMER-DISEASE; CELL-DEATH; **TRKB**
Research Fronts: 92-0319 006 (P75 NERVE GROWTH-FACTOR RECEPTORS; REGULATION OF NEUROTROPHIN MESSENGER-RNA **EXPRESSION**; DEVELOPING SENSORY NEURONS; RAT HIPPOCAMPUS)

6/3,K,AB/39 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3333361 IFI Acc No: 0017175
Document Type: C
NERVE GROWTH FACTOR/RECEPTOR COMPLEX; DETECTING NEUROTROPHIC FACTOR IN SAMPLE; INCUBATE CELLS THAT **EXPRESS** RECEPTOR PROTEIN WITH NEUROTROPHIC FACTOR, MONITORING TYROSINE PHOSPHORYLATION, COMPARE WITH

PHOSPHORYLATION IN CONTROL, PHOSPHORYLATION CHANGE INDICATES NEUROTROPIC FACTOR
Inventors: Kaplan David (US); Martin-Zanca Dionisio (ES); Parada Luis F (US); Soppet Dan (US)
Assignee: U S of America Health & Human Services
Assignee Code: 06814
Publication (No,Date), Applic (No,Date):
US 6071709 20000606 US 92890713 19920529
Publication Kind: A
Cont.-in-part Pub(No),Applic(No,Date): US 5231001 US 91668298 19910314
Priority Applic(No,Date): US 92890713 19920529; US 91668298 19910314

Abstract: The present invention relates to a complex comprising nerve growth factor (NGF) and trk proto-oncogene protein and a complex comprising neurotrophic factors, NT-3 or BDNF, and **trkB** protooncogene protein. The present invention also relates to methods for detecting the presence of NGF, NT-3 or BDNF neurotrophic factors and trk and trk-related proto-oncogene receptors. The present invention further relates to methods that may be used in diagnostics and therapeutics for **neurodegenerative** diseases such as Alzheimer's and Huntington's by detecting complexes comprising NGF or NGF related neurotrophic factors bound to the product of the tyrosine kinase trk or related trk proto-oncogene family member.

...DETECTING NEUROTROPHIC FACTOR IN SAMPLE; INCUBATE CELLS THAT **EXPRESS** RECEPTOR PROTEIN WITH NEUROTROPHIC FACTOR, MONITORING TYROSINE PHOSPHORYLATION, COMPARE WITH PHOSPHORYLATION IN CONTROL, PHOSPHORYLATION CHANGE...

Abstract: ...trk proto-oncogene protein and a complex comprising neurotrophic factors, NT-3 or BDNF, and **trkB** protooncogene protein. The present invention also relates to methods for detecting the presence of NGF...

...present invention further relates to methods that may be used in diagnostics and therapeutics for **neurodegenerative** diseases such as Alzheimer's and Huntington's by detecting complexes comprising NGF or NGF ...

Exemplary Claim: ...neurotrophic factor with reference to a control, comprising the steps of: a) bringing cells that **express** a **trkB**-proto-oncogene receptor protein into contact with a putative neurotrophic factor, wherein the contact is...

...c) comparing the amount of phosphorylation determined by step (b) with that of a control **trkB**-proto-oncogene receptor protein which is not contacted with the putative neurotrophic factor, whereby an...
Non-exemplary Claims: ...the step of bringing the cells into contact with orthophosphate, and in step (b), contacting **trkB**-proto-oncogene receptor protein with anti-**trkB** antibody to effect immunoprecipitation and measuring the amount of 3-orthophosphate incorporated in immunoprecipitated **trkB**-proto-oncogene receptor protein, whereby the measuring determines an amount of tyrosine phosphorylation of **trkB**-proto-oncogene receptor protein effected by step (a...

6/3,K,AB/40 (Item 2 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3287280 IFI Acc No: 0006376

Document Type: C
POSITIVE AMPA RECEPTOR MODULATION TO ENHANCE BRAIN NEUROTROPHIC FACTOR **EXPRESSION**; ADMINISTERING TO A MAMMAL AN AMOUNT OF ALPHA-AMINO-3-HYDROXY-5-METHYLISOXAZOLE-4-PROPRIONIC ACID (AMPA) RECEPTOR ALLOSTERIC UPMODULATOR; FOR **NEURODEGENERATION** WITHOUT LOSS OF MEMORY OR LEARNING; HUNTINGTON'S DISEASE ETC.; DOWN SYNDROME
Inventors: Gall Christine M (US); Lauterborn Julie C (US); Lynch Gary S (US); Vanderklish Peter W (US)
Assignee: California, University of Regents
Assignee Code: 13234
Publication (No,Date), Applic (No,Date):
US 6030968 20000229 US 97932746 19970917
Publication Kind: A
Calculated Expiration: 20170917
Priority Applic(No,Date): US 97932746 19970917

Abstract: Methods for increasing the level of neurotrophic factors and neurotrophic factor receptors in the brain of a mammal afflicted with a pathology which produces **neurodegeneration** without significant loss of memory or learning comprising administering to a mammal an effective amount of an allosteric upmodulator of alpha -amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid (AMPA) receptors.

POSITIVE AMPA RECEPTOR MODULATION TO ENHANCE BRAIN NEUROTROPHIC FACTOR **EXPRESSION**; ...

...OF ALPHA-AMINO-3-HYDROXY-5-METHYLISOXAZOLE-4-PROPRIONIC ACID (AMPA) RECEPTOR ALLOSTERIC UPMODULATOR; FOR **NEURODEGENERATION** WITHOUT LOSS OF MEMORY OR LEARNING; HUNTINGTON'S DISEASE ETC.; DOWN SYNDROME

Abstract: ...neurotrophic factor receptors in the brain of a mammal afflicted with a pathology which produces **neurodegeneration** without significant loss of memory or learning comprising administering to a mammal an effective amount...

Exemplary Claim: ...of neurotrophic factors in a brain of a mammal afflicted with a pathology which produces **neurodegeneration** without significant loss of memory or learning, said method comprising: administering to said mammal an amount of AMPA-receptor allosteric upmodulator effective to increase the **expression** of neurotrophic factors in said brain of said mammal.
Non-exemplary Claims: ...of increased neurotrophic factor receptors, wherein the mammal is afflicted with a pathology which produces **neurodegeneration** without significant loss of memory or learning, said method comprising: administering to said mammal an amount of allosteric upmodulator of AMPA receptors effective to increase the **expression** of said neurotrophic factor receptors...

...11. The method according to claim 8, wherein the neurotrophic receptor is the **TrkB** receptor...

...administering to said mammal an amount of AMPA-receptor allosteric upmodulator effective to increase the **expression** of neurotrophic factors in said nervous tissue...

6/3,K,AB/41 (Item 3 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

Dialog Acc No: 3050405 IFI Acc No: 9833714
Document Type: C
TRK TYROSINE KINASE RECEPTOR IS THE PHYSIOLOGICAL RECEPTOR FOR NERVE GROWTH

FACTOR; DETECTION OF ALZHEIMER'S AND HUNTINGTON DISEASES
Inventors: Kaplan David R (US); Parada Luis F (US)
Assignee: U S of America Health & Human Services
Assignee Code: 06814
Publication (No,Date), Applic (No,Date):
US 5817471 19981006 US 95480553 19950607
Publication Kind: A
Calculated Expiration: 20151006
Continuation Pub(No),Applic(No,Date): ABANDONED US 92885731 19920519
Cont.-in-part Pub(No),Applic(No,Date): US 5231001 US 91668298 19910314
Priority Applic(No,Date): US 95480553 19950607; US 92885731 19920519; US 91668298 19910314

Abstract: The present invention relates to a complex comprising nerve growth factor (NGF) and trk-proto-oncogene protein. The present invention also relates to methods for detecting the presence of NGF and trk-proto-oncogene receptor. The present invention further relates to methods that can be used in diagnostics and therapeutics for **neurodegenerative** diseases such as Alzheimer's and Huntington's by detecting NGF-trk receptor pairs and the phosphorylation of trk protein.

Abstract: ...present invention further relates to methods that can be used in diagnostics and therapeutics for **neurodegenerative** diseases such as Alzheimer's and Huntington's by detecting NGF-trk receptor pairs and...
Non-exemplary Claims: ...4. A method according to claim 1, wherein said trk-proto-oncogene receptor protein is **trkB**-proto-oncogene receptor protein...

...claim 1, wherein the source of the trk-proto-oncogene receptor protein is cells that **express** the receptor protein...

...10. The method according to claim 7, wherein said trk-proto-oncogene receptor protein is **trkB**-proto-oncogene receptor protein...

...claim 7, wherein the source of the trk-proto-oncogene receptor protein is cells that **express** the receptor protein...

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               $8.75  5 Type(s) in Format  4 (UDF)
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            $2.97    0.189 DialUnits File340
               $5.85  3 Type(s) in Format  4 (UDF)
            $5.85  3 Types
     $8.82  Estimated cost File340
            OneSearch, 5 files,  2.697 DialUnits FileOS
     $0.86  TELNET
    $94.30  Estimated cost this search
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$94.35 Estimated total session cost 2.920 DialUnits
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